Prostate cancer Research International:

Active Surveillance

(PRIAS)

Guideline and study for the expectant management of localized prostate cancer with curative intent

Study protocol

Version 5.0

November 27, 2014
Index

Introduction ........................................................................................................................................... 6
The biopsy protocol ................................................................................................................................. 7
   Biopsy protocol Active Surveillance study ............................................................................................... 8
   Repeat biopsy .......................................................................................................................................... 8
Criteria for inclusion ................................................................................................................................. 9
   Selection on the basis of survival ........................................................................................................... 9
   Biopsy Gleason score ........................................................................................................................... 9
   The reliability of the Gleason score ....................................................................................................... 9
   Biopsy results ........................................................................................................................................ 10
PSA density (PSA D) ............................................................................................................................... 11
   Life expectancy ..................................................................................................................................... 11
   Active Surveillance studies .................................................................................................................... 11
   Inclusion criteria for the Active Surveillance study ............................................................................... 12
   Exclusion criteria .................................................................................................................................. 12
Follow-up criteria for Active Surveillance ............................................................................................ 13
   Ad 1 Clinical progression ...................................................................................................................... 14
   Ad 2 Histological progression .............................................................................................................. 14
   Ad 3 Biochemical progression ............................................................................................................. 14
PSA doubling time (PSA DT) .................................................................................................................. 14
   Ad 4 Motivation of the patient ............................................................................................................... 15
   Moments of evaluation ......................................................................................................................... 15
   Frequency of visits ............................................................................................................................... 15
   Bone scan ............................................................................................................................................. 16
   ERSPC .................................................................................................................................................. 16
Study subjects .......................................................................................................................................... 17
   PSA velocity (PSA V) ............................................................................................................................ 17
   PSA D .................................................................................................................................................... 17
   Quality of Life ....................................................................................................................................... 17
   MRI ....................................................................................................................................................... 17
Practical aspects ....................................................................................................................................... 19
   Website (www.prias-project.org) .......................................................................................................... 19
   Questions and remarks ......................................................................................................................... 19
List of abbreviations ............................................................................................................................... 20
References ............................................................................................................................................... 21
Albertsen tables ..................................................................................................................................... 25
Abstract

Introduction
This protocol aims to provide an evidence-based guideline for the management of prostate cancer by Active Surveillance. This page holds its definition, the goal and the hypothesis, which will be tested in this study. An endpoint is defined as well. The following two pages show the biopsy protocol, the inclusion and exclusion criteria and the follow-up criteria. The pages thereafter give the evidence on which these criteria are based. If any questions arise, please find the contact details on page 19.

Definition
Active Surveillance manages selected men with prostate cancer expectantly with curative intent. This means men are carefully selected and subsequently actively observed in order to have the possibility to offer them curative treatment once the tumor seems to progress. The choice for Active Surveillance instead of watchful waiting is made by purpose, because watchful waiting is a rather confusing term due to the various intents of its participants. Not only men who can be managed with Active Surveillance can be watchful waiters, but those managed with palliative intent as well; for example because they are too sick or too old for curative treatment.

Goal
The goal of this study is to validate the treatment option Active Surveillance in men with localized, well differentiated prostate cancer, in order to limit the amount of overtreatment (i.e. treatments in men who are diagnosed with prostate cancer and would not have developed symptoms in the absence of screening). A number of subjects will be studied, such as PSA velocity (i.e. the absolute increase of PSA in a one-year time period), the pathological findings in radical prostatectomy specimens, and the effect of expectancy on the quality of life.

Hypothesis
Less than 5% of men managed by Active Surveillance will develop clinical progression (evidenced by a positive bone-scan) during their lifetimes.

Endpoint
The primary endpoint of this study is clinical progression, evidenced by metastasis (M1) on a bone scan. Secondary endpoints will be the number of men changing therapy, the behavior of PSA over time and the prostate cancer mortality.

Design
This is a prospective, observational study. Fixed criteria are used for inclusion and follow-up.
I Biopsy guideline for inclusion and repeat biopsy

Table 1

<table>
<thead>
<tr>
<th>Prostatic volume (cc)</th>
<th>Minimal number of biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-40</td>
<td>8</td>
</tr>
<tr>
<td>40-60</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>12</td>
</tr>
</tbody>
</table>

If the number of obtained biopsy cores is lower than the number stated in the table it is advised, but not obligatory to perform a repeat biopsy within 8 weeks after inclusion in this study.

II. Criteria for inclusion:

1) Histologically proven adenocarcinoma of the prostate.
2) Men should be fit for curative treatment.
3) PSA-level at diagnosis ≤ 10 ng/mL.
4) PSA density (PSA D) less than 0.2.
5) Clinical stage T1C or T2.
6) Gleason score 3+3=6.
7) One or 2 biopsy cores invaded with prostate cancer.
   a. If an MRI, including targeted biopsies on positive lesions, is done at inclusion, there is no limit in the number of positive cores (that is, more than two, and no limit in the % of cancer present in the cores).
   b. If saturation biopsies (either transperineal or transrectal) are done 15% of the cores can be positive with a maximum of 4. (i.e. <20 cores 2 cores can be positive (standard), 20-26 cores 3 cores can be positive, >26 cores 4 cores can be positive) (all other inclusion criteria still apply).
8) Participants must be willing to attend the follow-up visits.

Exclusion-criteria:

1) Men who can not or do not want to be radiated or operated.
2) A former therapy for prostate cancer.

III. Follow-up criteria for continuation of Active Surveillance:

1) Clinical: Clinical stage (cT) < 3
2) Histological: Gleason score 3+3=6
   None, one or two biopsy cores invaded with prostate cancer
3) Biochemical: PSA doubling time (PSA DT) > 10 years
   If PSA DT 0-10 years: repeat biopsy
   If PSA > 20 ng/mL: bone scan
4) Patient is content with active surveillance.
<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>0**</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>PSA-test</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DRE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biopsy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Repeat biopsy:

a) Standard after 1, 4, 7 and 10 year and subsequently every 5 years.
b) If PSA–DT is 0-10 years repeat biopsy every year is advised.

No more than 1 biopsy per year should be performed

** Time of diagnosis
Introduction

The increasing use of PSA as a screen test, the increasing number of biopsies, the increasing number of cores per biopsy and the increasing life expectancy has resulted in a more frequent diagnosis of prostate cancers, which are of lower grade and stage.\textsuperscript{1-3} The majority of these (screen-detected) prostate cancers have a good long-term survival, especially when only a small number of cores with well-differentiated prostate cancer is diagnosed.\textsuperscript{4, 5} Screening diagnoses prostate cancers which would not have been diagnosed in the absence of screening (i.e. overdiagnosis).\textsuperscript{6} The amount of overdiagnosis is subject to discussion; a proportion of 53\% was calculated by a computer model, using data from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC).\textsuperscript{1} In this study, men aged 55-75 are screened with a PSA threshold of 3.0 ng/mL (4.0 ng/mL before 1997). In essence, two types of curative treatment are, besides new minimally invasive treatments such as brachytherapy, HIFU and cryotherapy, available for men with localized prostate cancer, namely radical prostatectomy and radiotherapy. The therapy of choice is not only dependent on demographic and pathological aspects, such as PSA-level at diagnosis, biopsy Gleason score, clinical stage, age and comorbidity, but is also dependent on the favor of the patient. The goal of both treatments is to delete all vital tumor tissue. Unfortunately, both treatments can have toxic side-effects, which occur rather frequently and can be invalidating for the patient.\textsuperscript{7, 8}

The combination of these side-effects, the slow natural course of minimal prostate cancer, the frequent overdiagnosis, ethical aspects and costs have led to the understanding that it is essential to find out which men can be managed with Active Surveillance with possible deferred treatment and whom need immediate definitive treatment in order to prevent transition of overdiagnosis into overtreatment. The expectation is that a large number of men will not need any treatment; they will die of other causes. The strategy has failed if metastases developed despite stringent control and no curative treatment can be applied. The strategy can also be regarded as a failure if waiting with treatment leads to a dramatic decrease in the quality of life. However, the application of deferred curative treatment should not be regarded as a strategy failure.
The biopsy protocol

Prostate cancer is generally diagnosed by an ultrasound (TRUS) guided prostatic biopsy. The current literature has not reached agreement about the optimal number of cores which should be taken. Therefore, the pros and cons of the different biopsy-protocols are discussed. The majority of the recent publications on this subject indicate that a higher number of cores per biopsy results in better cancer detection.\textsuperscript{9-13} There is just one study which was not able to show a significant difference in cancer detection between 6 and 12 core biopsies.\textsuperscript{14} With a sextant biopsy, Presti et al. found a detection rate of 73\% in men who had a previously negative biopsy.\textsuperscript{13} The lateralized sextant biopsy is widely used nowadays.\textsuperscript{9} The detection rate increases to 85\% with this technique. A further increase in detection rate to 95\% can be achieved by taking an additional core midlobarly. Adding two extra cores to the octant biopsy does not result in a significant increase in detection rate. Chon et al. therefore recommend an octant biopsy.\textsuperscript{15}

The size of the prostate also influences the probability of finding a tumor. Vashi et al. have constructed a mathematical model to calculate the amount of cores needed to diagnose a tumor of certain size with 90\% certainty (table 3).\textsuperscript{12} For example: to diagnose a tumor with a volume of 1cc in a prostate of 20 grams with a probability of 90\%, a sextant biopsy would be sufficient, while 15 cores are needed to diagnose the same tumor in a prostate of 50 grams.

<table>
<thead>
<tr>
<th>Prostate Size (cc)</th>
<th>Tumor Vol. (cc)</th>
<th>0.1</th>
<th>0.3</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
<th>1.5</th>
<th>2.0</th>
<th>3.0</th>
<th>5.0</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>18</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>18</td>
<td>14</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>18</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3

With the increase of the size of the prostate, the detection rate of both the standard and the lateralized sextant biopsy decreases significantly. A recent paper shows the additional value of 10 over 8 cores per biopsy in prostates larger than 35 grams.\textsuperscript{16}
Biopsy protocol Active Surveillance study

Mainly based on the literature, but partly based on arbitrary decisions as well, we have chosen for the prostate size dependent protocol shown below:

Table 4

<table>
<thead>
<tr>
<th>Prostatic volume (cc)</th>
<th>Minimal number of biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-40</td>
<td>8</td>
</tr>
<tr>
<td>40-60</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>12</td>
</tr>
</tbody>
</table>

Repeat biopsy

A repeat biopsy is not advised if the number of obtained cores already matches the number of corresponding cores in the table. If not, it is advised, but not obligatory to perform a repeat biopsy within 8 weeks after diagnosis to obtain adequate sampling and thereby to prevent missing an aggressive Gleason pattern or a larger than expected tumor volume. If a higher Gleason pattern is found, this is likely not due to progression of disease, but more probable due to a sampling error in the first biopsy.\(^{18}\)
Criteria for inclusion

Selection on the basis of survival
The definition of Active Surveillance implies that included men should be able to receive curative treatment at any time during their disease. This implies that men should have an organ confined (clinical stage T1C or T2) prostate cancer at the time of inclusion. The Albertsen tables (addendum) give an idea of the survival of men with organ confined prostate cancer who were managed conservatively. The 20-year prostate cancer specific mortality for men with a Gleason score smaller than 6 varies from 4% to 15%, according to age at diagnosis. Although this proportion is 20% to 30% in men with a Gleason score 6 tumor, in men with Gleason score 7 disease already 40-75% decease as a result of prostate cancer. Moreover are these men less likely to die from other causes. The population that Albertsen et al. described was diagnosed before PSA was introduced. Therefore, 60% of men were diagnosed by transurethral resection of the prostate (TURP). As mentioned before, screening diagnoses prostate cancers earlier in their course, thus at younger age, and as a result the survival of men is likely to be longer.

The Partin tables give an estimation of the findings of the pathological specimen, based on the preoperative PSA-level and the biopsy Gleason score. Although it doesn’t give survival rates, men who are operated on and have a pathologically organ confined tumor with negative margins have a favorable survival chance. According to the Partin tables, the probability of having an organ confined tumor is much higher in men with biopsy Gleason score 3+3 than in those with a primary or secondary pattern 4 in the biopsy. Besides Gleason score, other predictors for organ confined disease are PSA level and clinical stage. The inclusion criteria for clinical stage and Gleason score we have chosen are mainly based on these data.

There is sufficient evidence that metastatic disease becomes more probable when the PSA-level is larger than 20 ng/mL. Performing a bone scan below this value is therefore not necessary.

Biopsy Gleason score
The Gleason score is based on the two most prevalent architectural patterns of malignant prostatic tissue. The Gleason patterns range from 1 to 5, being 5 the least differentiated pattern. Nowadays, most men diagnosed within the ERSPC have a Gleason score 3+3=6. A Gleason score of 4+3=7 is essentially different from 3+4=7, and has a different prognosis as well. It is therefore more informative to give both patterns, than just providing the sum of those (i.e. the Gleason-score).

The reliability of the Gleason score
Prostate cancer is a multifocal disease. It is likely that not all foci of prostate cancer are represented in the biopsy cores. There is also a chance that the most prominent Gleason pattern in the biopsy does not reflect the most prominent pattern in the radical prostatectomy specimen (reverse sampling). Furthermore, a Gleason pattern can be missed (sampling error) and differences between pathologists can occur (interobserver variability). These are all explanations for differences between the biopsy
Gleason score and the pathological Gleason score. It has therefore been questioned how representative a biopsy Gleason score is.

The gold standard for grading prostate cancer is the pathological Gleason score, derived from the radical prostatectomy specimen. Narain et al. showed that a biopsy Gleason score < 7 only leads to a pathological Gleason score < 7 in 54.8% of cases. The remainders were undergraded. Even though, the biopsy Gleason score is one of the most reliable prognostic factors for treatment and outcome. It was evidenced in the same paper that 88.8% of men with a biopsy Gleason score < 7 had no signs of prostate cancer recurrence.

The inter-observer variability that exists between pathologists for grading prostate cancer is mainly present in pathologists who were not specifically trained to score Gleason patterns. Renshaw et al. found a 78% difference for scoring Gleason score 7 between all-round pathologists and pathologists specially trained for urogenital diseases.

The prognostic value of the biopsy Gleason score is derived from multivariate analyses as well. It is therefore incorporated in all nomograms available. A man with a prostate cancer stage T1-T2, a PSA-level<10 and a biopsy Gleason score ≤ 6 for example has 98% chance not to die from prostate cancer in the next five years, according to the nomogram of d’Amico et al.

In the search for more reliable prognostic parameters for treatment decisions and follow-up, PSA derivates like the PSA density (PSA D), the PSA velocity (PSA V) and the PSA doubling time (PSA DT) have been described. Later on in this protocol, each of those will be discussed.

**Biopsy results**

With the assumption that the invasion of tumor in the biopsy cores is a reflection of the total tumor volume in the prostate, a prediction of the tumor volume in the prostate can be made. Not only the proportion of cancer invasion in the biopsies, but also the number of cores invaded with prostate cancer can be of help in the decision which treatment should be applied. The criteria of Epstein et al. use the proportion of prostate cancer in the biopsy as well; they postulated that men with a Gleason score ≤ 6, with two biopsies positive for prostate cancer with less than 50% invasion have a high probability (79%) to have a minimal focus of prostate cancer (≤ 0.5 mL). Therefore, every core of a biopsy should be handled and judged separately by the pathologist.
PSA density (PSA D)

The PSA D can easily be calculated by dividing the PSA level by the total volume of the prostate. A prostate larger than 40 cc. with a PSA level of 4.0 ng/mL has a PSA D of 4.0/40=0.10. A PSA D < 0.15 is correlated with a favorable biochemical progression free survival after radical prostatectomy. The mean PSA D of 120 watchful waiters, who were screen detected in the ERSPC with a PSA at diagnosis of < 10 ng/mL was 0.11 ng/mL/cc. (mean follow-up: 40 months, range 13-100). The PSA D is dependent on the way of measuring the prostatic volume. The most reliable way to do this is a planimetric volume measurement. Research from Rotterdam has shown that the interobserver variability of these measurements is only 13%. If planimetric volume measurement is not available, the volume can be calculated with the formula: volume = width * height * length * 0.52.

Life expectancy

The average life expectancy of men with an age over 50 is 28.0 years in the Netherlands. For men over 70, the life expectancy is 11.9 years.

Table 5

<table>
<thead>
<tr>
<th>Age</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>28.0 years</td>
</tr>
<tr>
<td>55</td>
<td>23.6</td>
</tr>
<tr>
<td>60</td>
<td>19.3</td>
</tr>
<tr>
<td>65</td>
<td>15.4</td>
</tr>
<tr>
<td>70</td>
<td>11.9</td>
</tr>
<tr>
<td>75</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Active Surveillance studies

Table 6 shows the inclusion criteria of published Active Surveillance/watchful waiting studies. The last two columns are reserved for this study and a randomized controlled multi-center trial, which is initiated by the National Cancer Institute and has to start inclusion in the near future.

Table 6

<table>
<thead>
<tr>
<th>Country</th>
<th>McLaren\textsuperscript{**}</th>
<th>Choo\textsuperscript{**}</th>
<th>Koppie\textsuperscript{**}</th>
<th>Stephenson\textsuperscript{**}</th>
<th>Zietman\textsuperscript{**}</th>
<th>Carter\textsuperscript{*}</th>
<th>PRIAS</th>
<th>START</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Canada (49-58)</td>
<td>Canada (49-84)</td>
<td>USA (44-87)</td>
<td>Canada (51-86)</td>
<td>USA (52-72)</td>
<td>USA (71)</td>
<td>USA (65)</td>
<td>NL (≥ 50)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>T1a-3c</td>
<td>T1b-2b</td>
<td>T1-2</td>
<td>T1a-3</td>
<td>T1a-2c</td>
<td>T1c</td>
<td>&lt;T3</td>
<td>≤ T2b</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>5.8 (0.2-21)</td>
<td>6.5 (0.3-14.6)</td>
<td>7.4 (Mean 12.3)</td>
<td>7.4 (0.9-25.2)</td>
<td>6.6 (&lt;20)</td>
<td>PSA D 0.19</td>
<td>PSA D &lt; 10</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Biopsy (No. of cores)</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Gleason score</td>
<td>2-7</td>
<td>3-7</td>
<td>2-10</td>
<td>2-10</td>
<td>≤ 8</td>
<td>4-6</td>
<td>≤ 3 + 3</td>
<td>≤ 6</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>WHO</td>
<td>WHO</td>
<td>WHO</td>
</tr>
<tr>
<td>Design</td>
<td>pro</td>
<td>pro</td>
<td>pro</td>
<td>pro</td>
<td>retro</td>
<td>pro</td>
<td>pro</td>
<td>RCT</td>
</tr>
<tr>
<td>N (Follow-up)</td>
<td>113 (14)</td>
<td>206 (33)</td>
<td>329 (33)</td>
<td>104 (33)</td>
<td>199 (33)</td>
<td>3,4 years</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Months</td>
<td>(0-58)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

pro: prospective study; retro: retrospective study; RCT: randomized controlled trial; PSA D; PSA density
Inclusion criteria for the Active Surveillance study

1) Histologically proven adenocarcinoma of the prostate
2) Men should be fit for curative treatment
3) Clinical stage T1C or T2
4) Gleason score $3+3 = 6$
5) One or 2 biopsy cores invaded with prostate cancer
   a. If an MRI, including targeted biopsies on positive lesions, is done at inclusion, there is no limit in the number of positive cores (that is, more than two, and no limit in the % of cancer present in the cores).
   b. If saturation biopsies (either transperineal or transrectal) are done 15% of the cores can be positive with a maximum of 4 (i.e. $<20$ cores 2 cores can be positive (standard), 20-26 cores 3 cores can be positive, >26 cores 4 cores can be positive) (all other inclusion criteria still apply)
6) PSA density (PSA D) less than 0.2
7) PSA-level at diagnosis ≤ 10 ng/mL
8) Participants must be willing to attend the follow-up visits

Exclusion criteria

1) Men who can not or do not want to be radiated or operated.
2) A former therapy for prostate cancer.
Follow-up criteria for Active Surveillance

1) Clinical:
   a. Clinical stage (cT) < 3
2) Histological:
   a. Gleason score 3+3=6
   b. One or 2 biopsy cores invaded with prostate cancer
3) Biochemical:
   a. PSA doubling time (PSA DT) > 10 years
   b. If PSA DT 0-10 years: repeat biopsy
   c. If PSA > 20 ng/mL: bone scan
4) Patient is content with active surveillance

Active Surveillance policy

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>0**</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>24</td>
<td>30</td>
<td>36</td>
<td>42</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>66</td>
<td>72</td>
<td>78</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA-test</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DRE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biopsy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Repeat biopsy:
1 or 2 cores with PC
AND
Gleason 3+3=6

Definitive curative treatment

End of study

Time table

Repeat biopsy indicated by time path

PSA-DT > 10 years

Clinical stage < T3

Metastases on bone scan

Continued on
Active Surveillance

Repeat biopsy:
1 or 2 cores with PC
AND
Gleason 3+3=6

Definitive curative treatment

End of study

Repeat biopsy indicated by time path

PSA-DT > 10 years

Clinical stage < T3

Metastases on bone scan

Standard after 1, 4, 7 and 10 year and subsequently every 5 years.
If PSA–DT is 0-10 years repeat biopsy every year is advised.
No more than 1 biopsy per year should be performed
** Time of diagnosis
Ad 1 Clinical progression

Digital rectal examination

The DRE has a high interobserver variability.\(^4\)\(^,\)\(^18\)\(^,\)\(^44\) In the different Active Surveillance studies, different thresholds for the clinical stage are used.\(^4\)\(^,\)\(^18\)\(^,\)\(^44\) In this study, a DRE is not obligatory at every visit, but only at evaluation visits. Clinical progression is defined as stage T3 or more (penetration of the capsule), irrespective of the initial clinical stage.

Ad 2 Histological progression

The proposed pattern for repeat biopsies is a one, four, seven, ten, fifteen and twenty years biopsy scheme. These moments are arbitrary and corroborate with the START study. The number of biopsy cores is again indicated by the biopsy protocol. Besides the standard biopsies, a repeat biopsy is necessary if the PSA DT is between three and ten years. No more than one biopsy per year should be obtained.

Ad 3 Biochemical progression

PSA doubling time (PSA DT)

PSA DT is defined as the time PSA needs to double its start-value. To preserve a difference in men who for example have a PSA of 2 and 10, the 2logPSA should be used. The PSA DT can subsequently be calculated by 1/slope. The slope denotes the slope through all 2log PSA values.

The use of PSA DT as a decision tool in this study is based on the observation that preoperative PSA levels are significantly correlated with the tumor volume in radical prostatectomy specimens.\(^52\) It is furthermore based on the knowledge that PSA values have an exponential course in individual non-treated patients.\(^53\) The PSA DT should therefore be linear.\(^54\) It is intuitively correct that the PSA DT is a good indicator for tumor growth, and this assumption is supported by studies which show that PSA DT is a strong predictor for the risk of metastases\(^55\) and death\(^56\) due to prostate cancer after radical prostatectomy or radiotherapy. McLaren et al. have shown that the PSA DT was the strongest predictor of clinical progression in conservatively treated men.\(^43\) Klotz described that in his Active Surveillance cohort the metastases free survival was 99% after 8 years. Initially, a PSA DT of less than two years led to curative treatment.\(^54\)

If prostate cancer is indeed clinically insignificant, the doubling time will be more alike that of men without prostate cancer. Prostate cancer with a PSA DT < 3 years is described to have a poor prognosis. Initially men on active surveillance were therefore advised to switch to active treatment if PSA DT < 3 years. However, analysis of the data collected during the past years showed that only approximately 30% of men directly followed this advice, the remaining 70% continued active surveillance. Men continuing active surveillance were at a higher risk of Gleason upgrading, but the majority of men did not progress.\(^63\) Men with a PSA DT < 3 years are therefore advised to have a repeat biopsy every year as with a PSA DT of 3 to 10 years. MRI with targeted biopsies or biopsies sampling the anterior part of the prostate could be considered to exclude large anterior tumors as a cause of the low PSA DT.
The PSA DT of 3 to 10 years range is unclear and needs further study. To minimize the chance on local progression, it is therefore advisable to perform a repeat biopsy in this range. A PSA DT larger than ten years suggests an indolent prostate cancer and therefore doesn’t need a repeat biopsy. The value of the PSA DT will be calculated by the web-based database. The Internet provides PSA DT calculators as well. (http://www.mskcc.org/mskcc/html/10088.cfm).

Ad 4 Motivation of the patient
It is known from the scarcely available studies that anxiety in patients is an important reason for choosing deferred curative treatment. This study provides the possibility of investigating this topic further by adding a quality of life component.

Moments of evaluation
It is unnecessary to calculate the PSA DT with every new PSA recording. The biological variation in serum PSA necessitates that calculation of PSA DT is based on several measurements. For this reason the annual moments of evaluation were invented. At the end of the first year, an evaluation on biochemical, clinical and histological progression can be made. By the end of the second year, the evaluation is based at least at the DRE and the PSA DT.

Frequency of visits
The argument for choosing a 3-monthly visit-schedule in the first two years and a semi-annual schedule thereafter is to recognize and filter out the fast growing tumors, which are not corresponding with the definition of clinically irrelevant tumors. Those are likely the tumors that were undersampled at diagnosis. By means of intensive control by repeat biopsy, 4 PSA recordings in the first year and a DRE men should be identified as not having irrelevant cancer. They would then have a therapy delay of a year. The literature which is available for such patients does not show a negative effect for this delay.

Table 9: follow-up parameters of published Active Surveillance studies

<table>
<thead>
<tr>
<th>Visit</th>
<th>McLaren**</th>
<th>Choo**</th>
<th>Stephenson**</th>
<th>Zietman**</th>
<th>Carter*</th>
<th>PRIAS</th>
<th>START</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PSA D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA DT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PSA V</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/t PSA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat biopsy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSA: prostate specific antigen
PSA D: PSA density (PSA/TRUS volume prostate)
PSA DT: PSA doubling time
F/t PSA: free to total PSA
TRUS: transrectal ultrasound

PSA V: PSA Velocity (absolute PSA-increase per year)
DRE: digital rectal examination
**Bone scan**

Active Surveillance has, different from watchful waiting, a curative purpose. The purpose of Active Surveillance is to wait with treatment, but to prevent the development of metastatic disease. It is evidenced that it is very unlikely for a bone scan to be positive with a PSA value under 20 ng/mL.\(^{23, 24}\) \(^{59, 60}\) The absolute PSA value was the best predictor for a positive scan. It is therefore that a bone scan is advised within this protocol if the PSA is higher than 20 ng/mL. If necessary, the bone scan results should be confirmed with X-ray.

**ERSPC**

In the first round of screening in the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC) 1,014 men were diagnosed with prostate cancer; 261 of them matched the inclusion criteria described in this protocol.

<table>
<thead>
<tr>
<th>Inclusion criterion</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{st}) round ERSPC</td>
<td>1,014</td>
<td>100</td>
</tr>
<tr>
<td>Age 50-75</td>
<td>980</td>
<td>99.2</td>
</tr>
<tr>
<td>PSA D &lt; 0,20</td>
<td>652</td>
<td>66.0</td>
</tr>
<tr>
<td>PSA &lt; 15 ng/ml</td>
<td>858</td>
<td>56.8</td>
</tr>
<tr>
<td>Gleason ≤ 3+3</td>
<td>621</td>
<td>62.9</td>
</tr>
<tr>
<td>≤ 2 cores with prostate cancer</td>
<td>496</td>
<td>50.2</td>
</tr>
<tr>
<td>All criteria</td>
<td>261</td>
<td>25.7</td>
</tr>
</tbody>
</table>

Table 10

Of those, 144 (39.8%) elected surgery, 108 (35.2%) elected radiotherapy, 1 man was treated with endocrine treatment and 63 were set on a watchful waiting policy. One man died (not from prostate cancer) before treatment had started.

<table>
<thead>
<tr>
<th>Watchful waiters</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Treatment at the end of the follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>2</td>
<td>3.2%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>11</td>
<td>17.5%</td>
</tr>
<tr>
<td>Watchful waiting</td>
<td>48</td>
<td>76.2%</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>2</td>
<td>3.2%</td>
</tr>
<tr>
<td>Last PSA</td>
<td>3,8</td>
<td>Range 1.8-14.0</td>
</tr>
<tr>
<td>Metastases</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Table 11
Study subjects

PSA velocity (PSA V)
PSA V is the absolute increase of PSA values in one year. A minimum of three measurements should be available with at least 3 months in between. A start PSA of 4 ng/mL, with values of 4.2 and 4.3 after three and six months has a PSA V of 0.3 in six months and thus a PSA V of 0.6 in one year. Carter et al. showed that 70% of men with prostate cancer and only 5% without prostate cancer had a PSA V less than 0.75 ng/mL/year. In ERSPC, this value is 0.62 ng/mL. A recent NEJM publication shows that a PSAV > 2.0 in the year before operation is a strong predictor for clinical progression and death due to prostate cancer. The results of this study are convincing. The reason we have not included PSA V as a decision tool is that only one study has proven this effect so far. It has to be validated in cohort studies and clinical trials before it can be used in clinical settings. We have included the PSA V as a subject of study.

PSA D
The value of PSA D as a decision parameter in the follow-up was not evident in published studies. Therefore, PSA D is a subject of study in this protocol and not a decision parameter.

Quality of Life
It is known from the scarcely available studies that anxiety in patients is an important reason for choosing definitive curative treatment. This study provides the possibility of investigating this topic further by adding a quality of life component. In a cohort (N=100) of men with prostate cancer on active surveillance in the PRIAS-study, questionnaires will be distributed three consecutive times, including questions on the choice for active surveillance, prostate cancer in general and mental and physical health. The first version (approx. 30 minutes) will be distributed in the period after inclusion in the study, the second and third (approx. 15 minutes) version after one and two year on surveillance.

MRI
The value of MRI and subsequent targeted prostate biopsies will be studied in the MRI PRIAS side study (see www.prias-project.org for study protocol). However, if as part of standard care MRI is performed, the data may be used for analysis in the current protocol. ASA-score
The ASA-score was originally designed to estimate the risk of anesthesia and surgery. It has been evidenced that this score can also be used for estimating the influence of comorbidity on the prognosis in men who are not operated.
ASA-score\textsuperscript{50}

<table>
<thead>
<tr>
<th>Class</th>
<th>Physical status</th>
<th>For example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A completely healthy patient</td>
<td>A fit patient with an inguinal hernia</td>
</tr>
<tr>
<td>II</td>
<td>A patient with mild systemic disease</td>
<td>Essential hypertension, mild diabetes without end organ damage</td>
</tr>
<tr>
<td>III</td>
<td>A patient with severe systemic disease that is not incapacitating</td>
<td>Angina, moderate to severe COPD</td>
</tr>
<tr>
<td>IV</td>
<td>A patient with incapacitating disease that is a constant threat to life</td>
<td>Advanced COPD, cardiac failure</td>
</tr>
<tr>
<td>V</td>
<td>A moribund patient who is not expected to live 24 hours with or without surgery</td>
<td>Ruptured aortic aneurysm, massive pulmonary embolism</td>
</tr>
</tbody>
</table>
Practical aspects

Website (www.prias-project.org)
Active surveillance patients will be managed on a website, which will give project documentation, store the inserted data at a central place, calculates parameters such as PSA DT and PSA D, gives protocolized advice to the physician and provides a printed documentation for the patient chart each time the patient attends the outward patient clinic for an evaluation visit. The information handling of patients is such that might the data become public, the information is useless and anonymized.

Questions and remarks
See www.prias-project.org for contact information.
List of abbreviations

ERSPC  European Randomized study of Screening for Prostate Cancer
PSA    Prostate-Specific Antigen
PSA D  PSA Density
PSA DT  PSA Doubling Time
TRUS   TransRectal UltraSound
References


36. Freedland, S. J., Csathy, G. S., Dorey, F. et al.: Clinical utility of percent prostate needle biopsy tissue with cancer cutpoints to risk stratify patients before radical prostatectomy. Urology, 60: 84, 2002

42. http://www.cbs.nl/:


Albertsen tables

Albertsen tables"