Prostate cancer Research International: Active Surveillance (PRIAS) MRI study

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SUMMARY

**Rationale:** Prostate cancer often has an indolent growth pattern. Radical treatment of these cancers therefore results in unnecessary side-effects and deterioration of quality of life. Active surveillance aims at postponing or even avoiding this radical treatment, without affecting oncological outcome.

The at the Erasmus MC initiated Prostate cancer Research International: Active Surveillance (PRIAS) study (METC Erasmus MC 2004-339, Dutch study title: “Active surveillance: Een afwachtend beleid met de mogelijkheid tot uitgestelde curatieve behandeling bij mannen met prostaatkanker; richtlijn en studie in de regio Rotterdam (PRIAS”) is currently the largest active surveillance study worldwide. Although short term results are promising, the selection of men with truly ‘indolent’ prostate cancer could be improved. Furthermore the criteria to switch to radical treatment are not optimal, with some men being treated unnecessarily and for some men treatment is deferred to long.

MpmMRI of the prostate with subsequent targeted biopsies could improve Gleason grading of the prostate cancer and therefore improve upfront selection and follow-up of men on active surveillance, further reducing the number of men with intermediate risk instead of low risk cancers selected initially for active surveillance. If mpmMRI with targeted biopsies improves Gleason grading, surrogate measures of Gleason progression currently used in the PRIAS study (more than 2 cores positive, PSA-DT <3 year) could be improved and replaced.

This side study of the PRIAS study aims at investigating the value of mpmMRI at inclusion and during follow-up of men on active surveillance.

**Objective:** To study the value of mpmMRI with subsequent targeted biopsies after inclusion to more accurately grade prostate cancers of men on active surveillance. Furthermore, the value of mpmMRI in reducing the number and amount of biopsies will be studied.

**Study design:** This side study of the PRIAS study is a prospective cohort study. Comparisons will be made with historically matched PRIAS participants. The study population will be offered a mpmMRI with subsequent targeted biopsies 3 months after inclusion in the PRIAS study and at every repeat biopsy during follow-up (year 1, 4 and 7) in
the PRIAS study. Men already included in the PRIAS study can be included in this side study at any point during the first 7 years of follow-up in the PRIAS study. The number of mpMRI's will depend on the time of inclusion in this side study.

**Study population:** The study population will consist of men with low-risk prostate cancer included in the PRIAS study who are willing and able to undergo mpMRI with subsequent targeted prostate biopsies.

**Study procedure:** Participants will be offered an mpMRI at inclusion and during following up. If mpMRI shows a suspicious lesion, additional targeted biopsies are taken on top of the standard TRUS guided biopsies. If participants have a low PSA-DT (<10 years, so fast increase of PSA) the currently used standard biopsy in addition to the 1, 4, and 7-year repeat biopsies is replaced with a mpMRI and only targeted biopsies if MRI-detected progression occurs (growth of a lesion and or increase of MRI-grade).

**Main study parameters/endpoints:** The main endpoint is the percentage of men upgraded (Gleason score ≥7) at inclusion and at repeat biopsies. Secondary endpoints are the therapy free survival rate, number of biopsies performed, biopsy complications, results after deferred radical treatment, development of metastasis and prostate cancer specific mortality.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The additional burden consist of a maximum of 7 mpMRIs during 7 years of follow-up and a maximum of 6 additional biopsies per repeat biopsy visit. Risk of MRI include allergy to contrast media. This risk is reduced as much as possible by excluding participants with a known contrast allergy. Studies have shown that taking additional biopsies during a biopsy procedure does not increase the risk of complications, except the pain that can be associated with the extra biopsies taken. On the other hand mpMRI could reduce the amount of repeat biopsy visits for some men with low PSA-DT. Furthermore it could improve the Gleason grading of the prostate cancer at inclusion, therefore better selecting men with true 'indolent' prostate cancer, and at follow-up reducing the amount of unnecessary radical treatments.
1. INTRODUCTION AND RATIONALE

Prostate cancer (PCa) is a major health problem, being the most frequent cancer among European men and the third most common cause of cancer death, after lung and colorectal cancer [1]. PCa is however a heterogeneous disease. Although some PCas behave very aggressive, leading to metastasis and eventually PCa death, most PCas (especially in the PSA era) have an indolent growth pattern. These cancers might never give rise to symptoms during lifetime if untreated. Radical treatment (surgery/radiotherapy) of such cancers results in unnecessary side effects and deterioration of quality of life.

For this reason active surveillance was introduced. In active surveillance, rather than immediately treating the disease actively, men are monitored closely, opting to defer treatment and preserve quality of life, meanwhile still being able to treat the disease well within the window of cure when progression occurs. In the last decade several active surveillance programs were initiated to prospectively study the feasibility and effectiveness of this treatment option. The at Erasmus MC, the Netherlands, developed Prostate cancer Research International: Active Surveillance (PRIAS) study (METC Erasmus MC 2004-339, Dutch study title: “Active surveillance: Een afwachtend beleid met de mogelijkheid tot uitgestelde curatieve behandeling bij mannen met prostaatkanker; richtlijn en studie in de regio Rotterdam (PRIAS)” ) is the largest active surveillance program worldwide, with over 3500 men included to date of which almost half in the Netherlands.

In the PRIAS study men with low-risk prostate cancer (defined as clinical stage T1c-T2, Gleason score 3+3=6, PSA <= 10.0ng/ml, PSA-density <0.2 ng/ml/ml and 2 or less biopsy cores invaded with prostate cancer) can be included on a website (www.prias-project.org). After inclusion men are followed according to a standard protocol with regular PSA testing, digital rectal examination (DRE) and prostate biopsies. Based on the results of these tests, men can continue on active surveillance or are advised to undergo deferred radical treatment (PRIAS study protocol available at www.prias-project.org).

Recently published short term results of the PRIAS study show active surveillance to be an attractive treatment option for low-risk PCa, with a radical therapy free survival rate of 77.3% at 2 years and no cancer specific mortality [2]. Despite these encouraging results, selection and follow-up of men on active surveillance could be improved. First, 31% of men treated with radical prostatectomy after a period of active surveillance (median 1.3 years) show
unfavorable outcomes (pT3-4 and/or Gleason score >=4+3) [3]. These men were most likely undersampled during inclusion and should not have been on active surveillance. This undersampling is a result of the currently used method to diagnose PCa (a random systematic transrectal ultrasound (TRUS) guided biopsy technique). This biopsy technique should therefore be improved to be able to better determine the highest Gleason grade of the PCa. Secondly, 35% of men treated with radical prostatectomy because of protocol advise do show favorable characteristics (Gleason score ≤ 3+3) [3]. The follow-up criteria to advise radical treatment used in the PRIAS study (Gleason score ≥ 7, more than 2 cores positive, PSA-doubling time (DT) < 3 years) are thus not optimal. Therefore during follow-up more accurate determination of the highest Gleason grade should be achieved. Surrogate endpoints of unfavorable disease (more than 2 cores positive, PSA-DT <3 year) could then be omitted, resulting in fewer men who are treated unnecessarily.

MpMR imaging of the prostate with subsequent targeted biopsies could help in improving both the accuracy of Gleason grading at inclusion and during follow-up. If MRI with targeted biopsies improves Gleason grading, surrogate measures of Gleason progression could be omitted. Several studies have shown that mpMRI is capable to distinguish potentially indolent PC from clinically relevant PC (defined as Gleason sum scores < 7 and 7 or higher)[4-7]. Furthermore, several studies showed MRI was able to improve selection of men suitable for active surveillance [8-12]. The role of MRI in the follow-up of active surveillance patients is less thoroughly studied and shows mixed results [13, 14]. Currently no major active surveillance protocols incorporate MRI as a standard inclusion or follow-up tool. Furthermore, it is unknown if MRI could be used to reduce the amount and frequency of biopsies done in men on active surveillance.

The proposed project studies the use of mpMRI in men on active surveillance at the start of active surveillance and during follow-up with the goal to more accurately grade PCa to select true low-risk PCa, reduce the number of biopsies and reduce the number of men with unnecessary radical treatment. The PRIAS study, being the largest PCa active surveillance study worldwide, offers a unique platform to do so.
2. OBJECTIVES

2.1 Primary objective

The main objective of this study is to study the value of mpMRI just after inclusion of men on active surveillance to achieve more accurate grading to select true low-risk PCa (Gleason score 6).

2.2 Secondary objective

The secondary objective is to reduce the number and amount of biopsies taken at inclusion and during follow-up of men on active surveillance.
3. STUDY DESIGN

This study is a prospective cohort study and is a side study of the PRIAS study. The cohort of men which will receive mpMRI’s during follow-up will be compared with a historically match cohort of men in the PRIAS study managed according to the current PRIAS protocol (see www.prias-project.org).

The proposed study allows participation of men during the first 7 years of follow-up in the PRIAS study. The number of mpMRI’s will depend on the moment of inclusion. Men included directly after inclusion in the PRIAS study will receive a mpMRI with subsequent targeted biopsies within 3 months of inclusion and at every repeat biopsy. Men included in this side study after already being 3 months on the PRIAS study will receive MRIs plus biopsies at every repeat biopsy. A flowchart of the side study and the current PRIAS protocol is given in figure 1.

The PRIAS study is a worldwide study with more than 100 participating centers in 17 countries. This side study will initially be carried out in the Erasmus MC in close co-operation between the departments of Urology and Radiology. Other PRIAS centers will however be invited to participate as well. Coordination for Dutch participating centers will be in the Erasmus MC.

The study protocol is planned for 7 years of follow-up. Evaluation of the results will be carried out after repeat biopsies are taken (year 1,4, and 7).
Figure 1. Flowchart MRI side studies:

1: Normal PRIAS
   - Follow-up according to normal PRIAS protocol
     - At repeat biopsy / during follow-up:
       - Gleason >=7 at repeat biopsy
       - More than 2 cores positive
       - PSA-DT < 3 year
     - Yes
   - No

2: MRI PRIAS side study
   - Active surveillance in PRIAS study
     - Yes
     - Suitable for MRI side study?
     - Yes
     - First follow-up visit (3 months) done?
     - Yes
   - No
   - MRI plus targeted biopsy at 3 months visit
   - Definitive therapy
     - No
   - Yes
   - MRI plus targeted biopsy at next repeat biopsy visit according to protocol
   - Follow-up according to normal PRIAS protocol
   - MRI plus targeted biopsies at biopsy visit 1,4,7 years
   - At repeat biopsy:
     - Gleason >=7 at repeat biopsy
     - More than 2 cores positive
     - PSA-DT < 3 year
     - Yes
   - No
4. STUDY POPULATION

4.1 Population (base)

The study population consists of men ≥18 years with low-risk prostate cancer included in the PRIAS study. In 2012 approximately 700 men were included into the PRIAS study worldwide.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1) Included into the PRIAS study <7 years ago
2) Men should be fit for curative treatment
3) Participants must be willing to attend the follow-up visits
4) Participants must be willing and able to attend follow-up MRIs and targeted biopsies

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1) Men who cannot or do not want to be irradiated or operated
2) A former therapy for prostate cancer
3) Men with a contraindication for MRI

4.4 Sample size calculation

In the currently used PRIAS protocol approximately 30% of men are reclassified at the 1 year repeat biopsy. To show a reduction in the MRI group to at least 15% with a type 1 error (α) of 0.05 and a power (1-β) of 80%, a minimum of 121 participants would be required assuming a binomial distribution [15].
5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The main endpoint is the percentage of men upgraded (Gleason score $\geq 7$) at inclusion and at repeat biopsies.

5.1.2 Secondary study parameters/endpoints

- Therapy free survival rate
- Percentage of upgraded (Gleason $\geq 7$) men positive on targeted biopsy versus random biopsy
- Number of biopsies performed
- Number and severity of biopsy complications
- Percentage favourable and unfavourable (pT3-4 and/or Gleason score $\geq 4+3$) pathological features at radical prostatectomy after a period of active surveillance.
- Biochemical recurrence rate after radical treatment
- Metastasis
- Prostate cancer specific mortality

5.1.3 Other study parameters

Parameters currently collected in the PRIAS study are: PSA, DRE, PSA-density, Charlson comorbidity index, age, free PSA, PSA-DT, Prostate volume, length, weight, number of biopsy cores taken and number of biopsy cores positive for prostate cancer. These parameters will also be used for this side study.

5.2 Randomisation, blinding and treatment allocation

No randomisation will be carried out.
5.3 Study procedures

5.3.1 Short summary of currently used PRIAS protocol

In the PRIAS study men with low-risk prostate cancer can be included according to the inclusion criteria (www.prias-project.org). Men are then regularly followed using PSA testing, DRE, and repeat biopsies according to the visit plan. Based on the results of these tests men can continue on active surveillance or are advised to switch to radical treatment (flowchart of follow-up criteria in figure 3).

5.3.2 MRI side study

The study procedure will be according to the normally used PRIAS protocol with addition/omission of the following:

- **At inclusion:**
  i. Men are offered a mpMRI at the 3 months PRIAS study visit.
  
  ii. If the mpMRI shows one or more suspicious lesions (defined as a PIRADS score ≥ 3 [16]), targeted biopsies should be taken. A maximum of 3 lesions (with the highest PIRADS score) are biopsied with a maximum of 2 biopsies per lesion. Targeting of MRI lesions can be done using three techniques: visual targeting (TRUS guided biopsy), software targeting (TRUS guided biopsy) or in-bore targeting (MRI guided biopsy), based on the technique available in the participating center.

  iii. If a targeted biopsy shows a Gleason score ≥ 7, men are advised to undergo definitive treatment.

  iv. The number of biopsy cores positive is not a criteria to switch to definitive treatment.

- **Repeat biopsy at 1, 4, and 7 year:**
  i. In addition to the standard TRUS guided biopsies for the PRIAS study a mpMRI is done two weeks prior to the biopsy procedure. If the mpMRI shows one or more lesions with a PIRADS score ≥ 3 targeted biopsies should be taken in addition to the standard TRUS guided biopsies. A maximum of 3 lesions (with the highest PIRADS score) are biopsied with a maximum of 2 biopsies per lesion. Targeting of MRI lesions can be done using three techniques: visual targeting (TRUS guided biopsy), software
targeting (TRUS guided biopsy) or in-bore targeting (MRI guided biopsy), based on the technique available in the participating center.

ii. If any of the biopsies show a Gleason score ≥ 7, definitive treatment is advised.

iii. The number of biopsy cores positive is not a criteria to switch to definitive treatment.

- **PSA-doubling time (DT):**
  
  i. A PSA-DT <3 years is not a reason for definitive therapy as it is in the PRIAS protocol.
  
  ii. Instead, if the PSA-DT is <10 years a yearly mpMRI is advised in the years no standard repeat biopsies is done.
  
  iii. Extra targeted biopsies are only taken if the mpMRI shows progression. Progression is defined as a higher overall PIRADS score of one or more lesions, more/new lesions with PIRADS ≥ 3 and/or growth of lesions as assessed by the radiologist. Only lesions that showed progression are biopsied with a maximum of 2 biopsies per lesion.
  
  iv. (If no prior MRI is available to assess progression, targeted biopsies are taken from a maximum of 3 lesions with a PIRADS score ≥ 3)

**Ad 1 Tumor Size on MRI**

There is no maximum tumor size to recommend definitive treatment.

**Ad 2 Size progression on MRI**

There is no clear definition of size progression specifically for evaluating prostate cancer growth. A definition used in general for the evaluation of solid tumors (Response Evaluation Criteria in Solid Tumors, RECIST) is as follows: Progression is defined as a 20% or more increase in the sum of longest diameters of measurable lesions (≥20mm). In addition the absolute increase should be at least 5mm [17]. This definition can be used as a guideline for assessing tumor progression.

Size progression itself in not a criteria for definitive treatment as the clinical significance is not yet well established.
Ad 3 Maximum number of lesions on MRI

There is no restriction to the maximum number of PIRADS ≥ 3 lesions visible on MRI to continue on active surveillance. Biopsies are targeted on the 3 lesions with the highest PIRADS score (most suspicious lesions).

Ad 4 Capsular invasion on MRI

Definition of extra-capsular invasion on MRI differs across literature. Definitions range from ‘indirect’ evidence of extra-capsular extension as abutment, irregularity of the capsule, neurovascular bundle thickening, bulging, and loss of capsule, to ‘direct’ evidence as measurable extra-capsular disease, and visible tumor outside the prostate [18]. Accurate determination of these signs of extra-capsular extension is dependent on the MRI protocol used, the experience of the radiologist and some subjective interpretation. Correlation with pathologic T3 disease, although dependent on the definition, is not perfect for either of the definitions [18-20]. Furthermore, the clinical relevance of, especially minimal, extra-capsular extension is not well known. It was therefore decided that extra-capsular extension on MRI is not a protocol based reason for definitive curative treatment. Staging of prostate cancer remains on the basis of the DRE.

Flowchart of the follow-up criteria and the follow-up visits are shown in figures 2 and 3.

MRI visit scheme:

- Two weeks prior to a biopsy visit an mpMRI is done and blood is drawn for PSA testing.
- Evaluation of mpMRI is done by a radiologist, who selects a maximum of 3 lesions with PIRADS score ≥3 (if more lesions, select lesions with highest PIRADS score).
- Biopsy visit: During a biopsy visit standard DRE and TRUS guided biopsies according to volume are done (no standard biopsies will be taken in this side study at the 3 months MRI). MRI guided biopsies are taken during the same visit if applicable (maximum 2 per lesion).
- Two weeks after the biopsy visit evaluation of all results according to follow-up criteria is done.
## Figure 2. Follow-up visits

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
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<td>Month</td>
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<td>6</td>
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<tr>
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<td>X</td>
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<tr>
<td>Side study</td>
<td>MRI + targeted biopsies**</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></td>
<td>Evaluation</td>
<td>X*</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

* MRI 3 months after diagnosis: only targeted biopsies if lesion is visible on MRI (maximum of 3 lesions (2 biopsies per lesion)), no standard TRUS guided biopsies.

** If PSA-doubling time <10 years: A MRI is recommended every year (only in the years no standard biopsy is taken). Additional biopsies are indicated if MRI shows PIRADS progression, more lesions or growth of currently known lesion(s).
Figure 3. Follow-up Criteria PRIAS and side study:

Active surveillance

<table>
<thead>
<tr>
<th>PSA &lt; 20 ng/ml</th>
<th>No</th>
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<table>
<thead>
<tr>
<th>Clinical stage &lt; cT3</th>
<th>No</th>
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| PSA DT > 3 years | Yes |

Repeat biopsy indicated by time path?

| Yes |

<table>
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<tr>
<th>PSA DT &gt; 10 years</th>
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</table>

Definitive therapy

| MRI every year: PIRADS progression, more lesions or growth of known lesion |

| Yes |

End of study

| Yes |

<table>
<thead>
<tr>
<th>Metastases on bone scan?</th>
</tr>
</thead>
</table>

| Yes |

| MRI scan: if PIRADS ≥ 3, extra targeted biopsy |

| Yes |

| Repeat biopsy (+ targeted biopsy if PIRADS ≥ 3): |
| Maximal 2 cores with PC AND Gleason score 3+3 |

| Yes |

| No |

Continue active surveillance

| Yes |

| No |

| No |

| No |

| No |

| No |
6. REFERENCES


