



Editorial

Prospective Validation of Active Surveillance in Prostate Cancer: The PRIAS Study

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The incidence of prostate cancer (PCa) has risen in most Western and Eastern countries during the last 15 yr. Most detected tumours have a lower grade and stage than in the past. The increasing number of biopsies, the increasing number of cores per biopsy, the increasing overall life expectancy, and most importantly, the increasing use of prostate-specific antigen (PSA) measurements as screening tests, with lower thresholds for biopsy, account for this development [1]. The majority of these screen-detected tumours have favourable characteristics, with a beneficial long-term survival [2]. Many of these malignancies would most probably not have caused any symptoms during a man's lifetime if they had remained undiagnosed. This so-called over-diagnosis due to screening often results in over-treatment, subjecting men to unnecessary costly and invasive treatment with the risk of important side-effects [3,4]. Men screened for PCa should be protected against this. The replacement of initial active treatment with active surveillance in patients with small, localised, well-differentiated PCa contributes to achieving this aim. Quality of life might also be preserved longer with this strategy. Because screening for PCa is frequently applied, the attention to this approach in this specific subgroup of men with PCa has increased. There is a rising demand for an evidence-based approach, but unfortunately it is not yet available. Uncertainties currently exist concerning the risk of missing the

window of curability in PCa and criteria to rely on for changing from active surveillance to curative therapy in time to avoid or minimise that risk [5].

The Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) [6] and the Department of Urology of the Erasmus Medical Center in Rotterdam have initiated the prospective, observational Prostate Cancer Research International: Active Surveillance (PRIAS) study to validate the management of PCa with active surveillance. A previous article shows that retrospectively 261 of 1014 men (25.7%) with PCa detected in the first round of screening in the Rotterdam section of the ERSPC were suitable for active surveillance, when applying the clinical, histologic, and biochemical criteria used in the PRIAS study, which are described below. In practice in only 64 of these 261 men (24.5%) was a watchful strategy chosen [7]. In patients in whom active surveillance was actually elected, a very beneficial outcome was observed, with a cause-specific survival of 100% [8].

The PRIAS study is entirely Web based. The Web site (www.prias-project.org) offers patients information on the study and after login can be used by physicians to enter patient inclusion and follow-up data. Using this tool offers many benefits for daily urologic clinical practice. Each time the urologist enters data of a follow-up visit, a graph survey of the PSA measurements is presented and the PSA doubling time (PSADT) is calculated. Furthermore,

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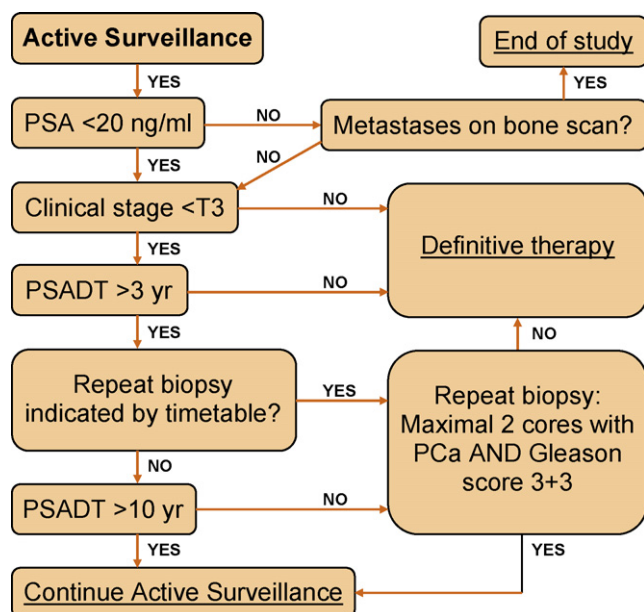


Fig. 1 – Follow-up criteria decision tree. PSA = prostate-specific antigen; PSADT = PSA doubling time; PCa = prostate cancer.

based on the follow-up criteria (Fig. 1), a recommendation is automatically presented on whether the patient should continue on active surveillance or whether to discontinue and opt for active treatment (Fig. 2). Most importantly, the Web site offers support in clinical practice by facilitating evidence-based decisions when considering active surveillance.

With the inclusion criteria of the PRIAS study (Table 1), an attempt is made to select men with insignificant organ-confined tumours who have a favourable prognosis [9–13]. The criteria are: (1) men should have a histologically proven adenocarcinoma of the prostate, and they should be fit for possible curative treatment, be willing to attend the follow-up visits, and should not have received former therapy; (2) clinical stage is T1C or T2; (3) Gleason score is ≤6 and two or fewer biopsy cores must be invaded with PCa; (4) PSA is ≤10 ng/ml and

Table 1 – Inclusion criteria

<p>1. Men should:</p> <ul style="list-style-type: none"> – Have histologically proven adenocarcinoma of the prostate – Be fit for curative treatment – Be willing to attend the follow-up visits – Not have received former therapy for prostate cancer <p>2. Clinical stage is T1C or T2</p> <p>3. Gleason score is ≤6 and ≤2 biopsy cores are invaded with prostate cancer</p> <p>4. PSA is ≤10 ng/ml and PSA density is ≤0.2 ng/ml/ml</p> <p>PSA = prostate-specific antigen.</p>
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PSA density is ≤0.2 ng/ml/ml. The percentage of cancer invasion in a biopsy core has not been taken up in our present inclusion criteria, although it does provide additional information on the probability of the presence of a minimal focus of prostate cancer [14]. It is currently not a standard procedure in all centres for pathologists to evaluate each specific core in this detail. Implementation of this criterion at this time would therefore strongly reduce the general feasibility of and participation in our protocol.

The follow-up protocol, combining visits according to a timetable with standardised follow-up criteria, is formulated to detect in a timely manner the fast growing tumours, which are aggressive and therefore not suitable for active surveillance.

The timetable consists of PSA measurements every 3 mo and biannual clinical examinations during the first 2 yr and biannual PSA measurements and annual clinical examinations in the subsequent years. Repeat biopsies are standard and are planned after 1, 4, 7, and 10 yr of surveillance. These are essential to correct for possible under-sampling during the initial biopsies and to detect true progression of tumour grade [15,16].

The follow-up criteria of the PRIAS study are: (1) patient is content with active surveillance; (2) clinical stage remains <T3; (3) Gleason score remains ≤6 and two or fewer of the repeat biopsy cores are invaded with prostate cancer; (4) PSADT is favourable and remains longer than 3 yr. A PSADT <3 yr is considered unfavourable and leads to the advice to opt for deferred active treatment. If the PSADT is in the ‘grey’ area between 3 and 10 yr, it is recommended to perform a repeat biopsy additional to the standard protocol, unless this is already indicated in the same year according to the timetable [17,18]. Decisions on continuing or discontinuing active surveillance are based on the value of the PSADT only after a patient has been in the study during a full year. A reliable estimate of the PSADT can then be made, based on five single PSA measurements. Later on during follow-up, the physician can select the PSA measurements on which the calculation of the PSADT is based. Whenever the serum PSA exceeds 20, a bone scan is advised [19].

When taking biopsies in a PRIAS study candidate, it is advised to use the guideline for the number of biopsy cores to be taken in a certain prostate volume (8 in <40 cc, 10 in 40–60 cc, and 12 in >60 cc) [20,21]. If the number of obtained biopsy cores used for inclusion is lower than instructed it is advised, not obligatory, to perform a repeat biopsy within 8 wk after inclusion.

At this moment the PRIAS study is applied in a collaborative effort among centres in the region of

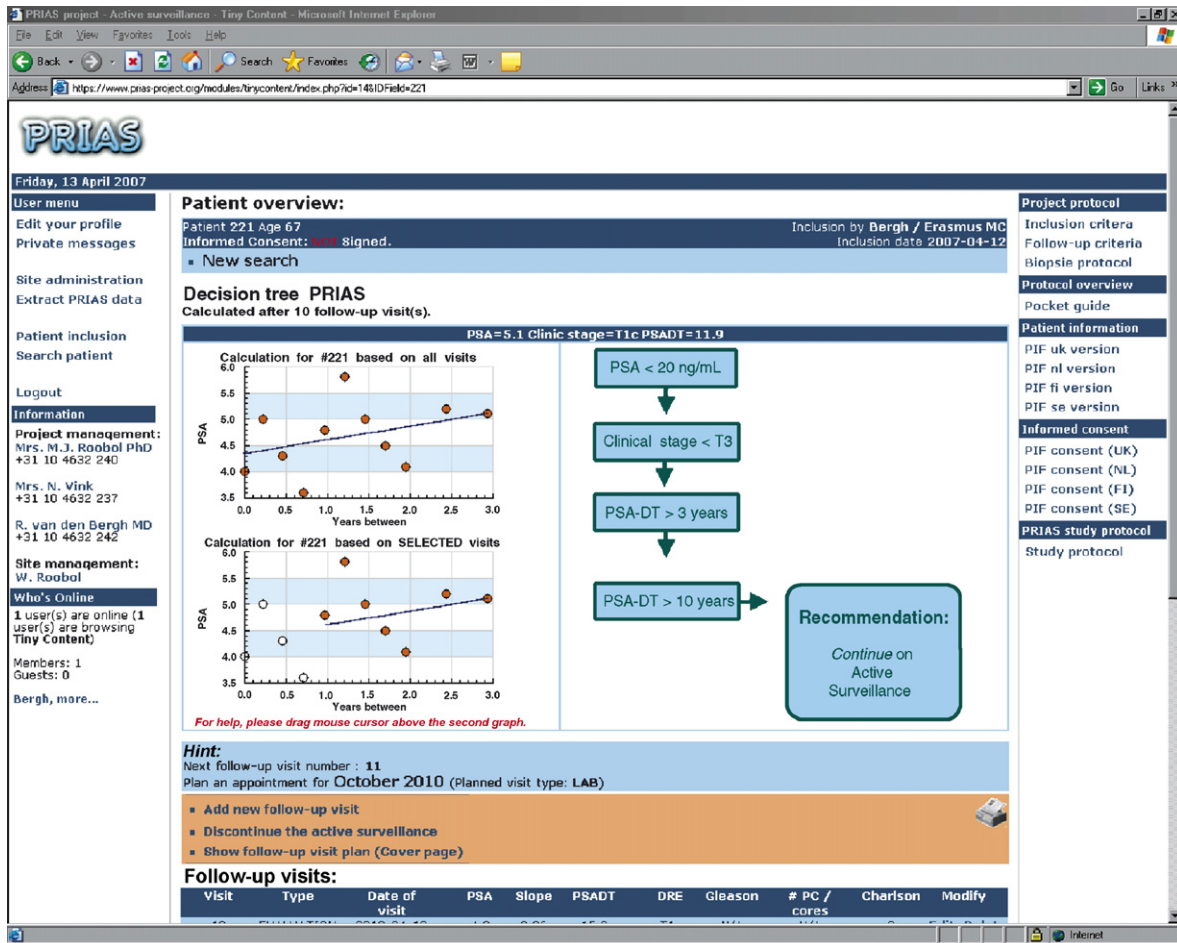


Fig. 2 – Screen shot of the Web site www.prias-project.org.

Rotterdam, The Netherlands and in Helsinki, Finland. Soon the application of the protocol will be extended internationally, including North America. The aim of the study is to provide a highly needed evidence-based guideline for active surveillance in PCa to prevent over-treatment. Future results can be used to study PSA changes (PSADT, PSA velocity, PSA density) and pathologic findings in radical prostatectomy specimens of patients with PCa considered suitable for active surveillance. With longer follow-up, the data can be related to hard end points such as clinical progression and cancer-specific survival. Furthermore, the effect of active surveillance on the quality of life and the validity of the use of a Web-based decision tool in actively surveying patients with PCa are investigated.

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