Prostate Cancer Detection and Dutasteride: Utility and Limitations of Prostate-Specific Antigen in Men with Previous Negative Biopsies

Pim J. van Leeuwen a,*, Konrad Kölble b, Hartwig Huland c, Thomas Hambrock d, Jelle Barentsz d, Fritz H. Schröder a

a Department of Urology, Erasmus University Medical Centre, Rotterdam, The Netherlands
b Institut für Pathologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
c Prostata Krebszentrum am Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
d Department of Radiology, St. Radboud University Medical Centre, Nijmegen, The Netherlands

Abstract

Context: We addressed the question whether the change of serum prostate-specific antigen (PSA) in men who use 5α-reductase inhibitor (5-ARI) dutasteride is sensitive for the detection of aggressive prostate cancer (PCa).

Objective: The case of a man using dutasteride diagnosed with Gleason 7 transition zone cancer at biopsy indicated by a rising PSA is described. The following issues are discussed: (1) Is a rise of PSA in patients using dutasteride predictive of aggressive PCa in men with prior negative biopsies? (2) Is it safe not to biopsy men using dutasteride who do not show a rising PSA? (3) How can we avoid potentially unnecessary biopsies in men using dutasteride without a rising PSA?

Evidence acquisition: We reviewed the recent literature addressing our objective that relates to two studies: the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial.

Evidence synthesis: In men using dutasteride, the positive predictive value/detection rate of Gleason 7–10 PCa is 13.2% and 4.0% for men with and without a rising PSA, respectively. However, a substantial proportion of Gleason 7–10 cases (42.9%) would be missed if a rising PSA was used as the only biopsy indication. Currently available data do not provide selective mechanisms to diagnose these cancers.

Conclusions: A rising PSA for a patient using dutasteride should be an indication for prostate biopsies. Currently, in the case of stable PSA a biopsy may still be considered. Options for a selective approach are therefore suggested in this review to avoid unnecessary biopsies and to achieve a more selective PCa detection in men on 5-ARI treatment.

© 2010 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Erasmus MC, University Medical Centre, Room NH 227, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Tel. +31107032242; Fax: +31107035315.
E-mail address: p.vanleeuwen@erasmusmc.nl (P.J. van Leeuwen).
1. Introduction

In December 2003, a white man 66 yr of age was referred to our hospital by his general physician with an elevated serum prostate-specific antigen (PSA). The patient’s medical history was unremarkable. He revealed no urinary complaints and reported he was sexually active with good erectile function. Serum analysis showed a serum PSA of 5.9 ng/ml. A complete physical examination showed no abnormalities; digital rectal examination (DRE) revealed an enlarged symmetric benign prostate gland. A transrectal ultrasound (TRUS) was performed using an 1846 mainframe (Bruel & Kjaer, Glostrup, Denmark) with a 7-MHz biplanar endorectal transducer. The TRUS showed no areas that were suspicious for prostate cancer (PCa); a total prostate volume of 55.0 ml was measured. TRUS-guided lateral sextant biopsies were taken from the base, midpart, and apex sections of the prostate. Histologic examination revealed no PCa or inflammation.

The patient was followed every 6 mo by measuring serum PSA and performing a DRE. At the end of 2004, when the serum PSA was 6.3 ng/ml, we advised the patient to start with a daily dose of dutasteride 0.5 mg. Subsequently, the serum PSA decreased by 38% to 3.9 ng/ml under dutasteride. Fig. 1 shows the patient’s complete PSA history. Up to May 2009, the patient was followed every 6 mo with a DRE and PSA measurement. In May 2009, the serum PSA had increased to 5.9 ng/ml, and a suspicious lesion in the right lobe was felt at DRE for the first time and classified as cT2a. In November 2009, 5 yr after starting dutasteride, this cT2a lesion was confirmed, and the serum PSA had increased to 6.3 ng/ml. A TRUS of the prostate was repeated showing a 42.8 ml prostate volume without any suspicious areas. A total of eight TRUS-guided biopsies were taken from the lateral base, midpart, and apex sections of the prostate (mean length of biopsies: 16 mm). Histologic examination showed no PCa or inflammation.

Six months later, the serum PSA had further risen to 6.6 ng/ml, which led to the recommendation of a multimodality 3-T magnetic resonance imaging (MRI) to identify or rule out a region suspicious for PCa. T2-weighted imaging in the axial, sagittal, and coronal plane was performed for anatomic visualisation of the prostate. Functional MRI techniques that included diffusion-weighted imaging (DWI) and pharmacokinetic dynamic contrast-enhanced (DCE)-MRI were also obtained. DCE-MRI was performed following administration of 15 ml gadolinium dimeglumine (Dotarem, Guerbet, France). The scanner software automatically calculated apparent diffusion coefficient maps from the DWI using b-values of 0, 50, 500, and 800. From the combined information obtained from all three imaging modalities, a dominant lesion, highly suspicious of PCa, was identified in the very cranial part of the left transition zone extending toward the bladder trigone (Fig. 2). The features on MRI were consistent with intermediate- to high-grade PCa (Gleason score ≥7). MRI revealed a prostate volume of 41.3 ml. Following this, two lesion-targeted biopsies (mean length: 15.5 mm) were obtained using an MR-compatible biopsy device (Invivo, Schwerin, Germany). Both biopsies showed adenocarcinoma, Gleason score 3 + 4 = 7, in 40% and 5% of the total biopsy volume, respectively. MRI showed no extracapsular extension, and the tumour was classified as T2a. Due to the difference in location, this lesion was obviously not compatible with the T2a lesion suspected on DRE. The patient was still in good condition, classified as American Society of Anaesthesiologists class 1.

A decision was made to perform an open retropubic radical prostatectomy, with bilateral lymph node resection and preservation of both neurovascular bundles. Based on the findings on MRI, it was decided to remove part of the left trigone of the bladder where the MR images revealed close proximity of the tumour to the bladder base (Fig. 2). Intraoperative frozen section examination showed PCa at the left prostatic base extending into the detrusor muscle without infiltration of the urinary bladder mucosa. All resection margins and regional lymph nodes were negative. The prostatectomy specimen, weighing 40 g, was submitted in its entirety and showed moderately differentiated adenocarcinoma located primarily in the left transition zone of the prostate. Three additional foci of adenocarcinoma, measuring <5 mm and representing <20% of the total cancer volume, were detected in the left apex and anterolaterally. The tumourous regions of gross transverse and perpendicular sections are mapped in Fig. 3. All foci were Gleason 3 + 4 = 7 with a Gleason 4 fraction of 10%. The largest lesion in the transition zone had a diameter of 32 mm. The total tumour volume was 4.67 ml. No invasion of periprostatic fat or seminal vesicles was detectable. All

---

Fig. 1 – Complete history of all serum prostate-specific antigen (PSA) measurements during observation before diagnosis of prostate cancer (PCa). The start of taking a daily dose of dutasteride 0.5 mg and the two series with negative prostate biopsies (Bx) are indicated.
resection margins and all of the 19 regional lymph nodes resected were confirmed to be negative. Final TNM staging (7th edition, 2009) was pT3a, pN0, R0. The patient’s postoperative recovery was uneventful. Three months after surgery the patient is doing well without any sign of recurrence, urinary incontinence, or erectile dysfunction. The PSA level has decreased to <0.1 ng/ml.

This paper will not only put the case just described into a broader perspective, but it will also address the issue of the value of PSA and other possibly available clinical parameters to identify PCa in men using dutasteride after a previous negative biopsy for the exclusion of PCa. This should enhance our understanding of dutasteride use and the detection of PCa in men with prior negative biopsies. The following key issues are addressed:

- Which clinical action should be taken in case of a rising PSA under dutasteride treatment?
- What if PSA does not rise under dutasteride treatment in men with a previous negative biopsy?
- Can dutasteride use in men with previous negative biopsies help avoid potentially unnecessary biopsies?

2. Evidence acquisition

In the Prostate Cancer Prevention Trial, 18 882 men ≥55 yr with PSA values ≤3.0 ng/ml and normal DREs were randomly assigned to treatment with a 5α-reductase inhibitor (5-ARI), finasteride, or placebo. After 7 yr of follow-up the trial showed a statistically significant reduction of positive biopsies, either taken “for cause” or as the end of study biopsies that were offered to all participants in both treatment groups. The trial not only showed a 24.4% relative reduction in the prevalence of positive biopsies but also a significant increase in aggressive cancers classified as Gleason 7–10 [1]. It was shown that the use of finasteride increased the sensitivity of detecting PCa [2,3] and of identifying high-grade PCa [4].

The second important study, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, addressed in greater detail later, also showed a significant reduction in positive prostate biopsies using dutasteride for 4 yr [5]. Recently published data provide more details on the incidence and characteristics of PCa detected in both arms, with and without rising PSA values [6]. In this paper we analyse the potential clinical value of a rising or stable PSA under dutasteride treatment in men who have had a previous negative biopsy. To achieve this goal and to put our discussions into proper perspective, it is necessary to reiterate some of the aspects of the design and results of the REDUCE trial.

The rationale and design of the REDUCE trial is described in Andriole et al. [7]. In this prospective randomised placebo-controlled study of dutasteride [5], a dual-action 5-ARI, 6729 men 50–75 yr of age who had a previous negative prostate biopsy indicated for PSA values between 2.5 and 10 ng/ml were randomised. Investigators were blinded to the PSA values during the 4-yr follow-up but were informed of a doubling of PSA values and were allowed...
to maintain their own PSA-based follow-up. Men were followed every 6 mo by PSA testing and DRE. According to the protocol, 10 core biopsies were carried out after 2 and 4 yr independent of PSA values, and 82.8% of the men had at least one biopsy. The proportion of men in the dutasteride and placebo arms who received protocol-independent biopsies amounted to 4.1% and 4.8% during months 1–18 of follow-up and 4.4% and 6.7% during months 25–42; 16.6% and 16.7% of protocol-independent biopsies revealed tumour in the dutasteride and placebo groups of which 7.1% and 5.6% were classified as Gleason 7–10, respectively. The overall outcome of the trial revealed a statistically significant relative reduction in the rate of positive biopsies of 22.8%. The reduction was due to finding fewer well-differentiated (Gleason 6) cases of PCa. There was no significant increase but a trend toward finding more Gleason 7–10 cancers in the dutasteride arm. There were, however, 12 Gleason 8–10 cancers in the dutasteride arm as opposed to only 1 in the placebo arm (p = 0.003). Table 1 provides further details of the overall outcome of the REDUCE study. The data relate to the efficacy population of the trial, which took into account the exclusions due to not receiving the drug, a positive baseline biopsy, and the lack of biopsy reviews. In the table, the segments "PCA all" and "PCA years 3 and 4" relate to those who were biopsied during the whole study period and during or after years 3 and 4. The table then shows the rates of aggressive cases of PCa identified in the two study arms overall and during the years 3 and 4. These data are the basis for the subsequent discussion of the recent publication on the usefulness of PSA in diagnosing high-grade cancers under dutasteride in comparison with placebo [6].

Fig. 3 – Radical prostatectomy specimen after gross transverse (central) and perpendicular (apex and base) sectioning. Mapped regions of adenocarcinoma are outlined in red. All four discernible foci (F1–F4) were Gleason 3 + 4 = 7.
3. Evidence synthesis

3.1. Which clinical action should be taken in men with previous negative biopsies and rising prostate-specific antigen with dutasteride treatment?

In patients with benign prostatic hyperplasia (BPH), 5-ARIs effectively suppress serum PSA levels by about 50% over periods of 4 and 7 yr [1,5]. However, the presence of PCa in those men cannot be excluded. There is now agreement that 5-ARIs suppress the progression of well-differentiated disease rather than acting as primary prevention [5,8]. This implies that well-differentiated (Gleason 6) cancers can be assumed to still be present in the prostates of men who are treated with 5-ARIs. On the other side of the spectrum, it is likely that 5-ARIs are not capable of suppressing most aggressive cases of PCa. In the REDUCE trial overall, the proportion of Gleason 7–10 and 8–10 cancers do not differ significantly between treatment arms as shown in Table 1. This suggests that dutasteride neither stimulates nor suppresses cancers in these Gleason categories. A rise of PSA under dutasteride treatment is therefore suggestive of the presence of aggressive PCa. The relevant data on this issue from Andriole et al. [6] are summarised in Table 2. If we would decide to biopsy only those cases who have a rising PSA, we would identify 124 of the 217 Gleason 7–10 cancers (57.1%). This leads to a detection rate (equal to the positive predictive value [PPV] in this setting) of 13.2%, which is 3.3 times higher than the similar figure in those men who do not have an increase in PSA. This figure almost doubles the rate of detection of aggressive cancers with respect to the control arm (13.2% vs 7.7%). These data leave

<table>
<thead>
<tr>
<th>Table 1 – Prostate biopsies, prostate-specific antigen change and detection of all versus aggressive cancers in the “efficacy population” of the REDUCE trial [5,6]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dutasteride</strong></td>
</tr>
<tr>
<td><strong>Participants (efficacy population)</strong></td>
</tr>
<tr>
<td>Biopsied all (percentage of efficacy population)</td>
</tr>
<tr>
<td>Biopsied year 3 + 4 (percentage of efficacy population)</td>
</tr>
<tr>
<td>Biopsied “for cause” (percentage of all biopsied)</td>
</tr>
<tr>
<td>PSA rise (6–48 mo) (percentage of all biopsied)</td>
</tr>
<tr>
<td>Years 1–4 PCa all (percentage of all biopsied)</td>
</tr>
<tr>
<td>PCa Gleason 7–10 (percentage of all biopsied)</td>
</tr>
<tr>
<td>Years 3 and 4 PCa all (percentage of all biopsied)</td>
</tr>
<tr>
<td>PCa Gleason 7–10 (percentage of all biopsied)</td>
</tr>
</tbody>
</table>

PCA = prostate cancer; PSA = prostate-specific antigen; REDUCE = Reduction by Dutasteride of Prostate Cancer Events trial.

<table>
<thead>
<tr>
<th>Table 2 – Detection of all and aggressive cancers in men with and without a rise of prostate-specific antigen during the 4-yr study period of the REDUCE trial [6] and performance of the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No increase</strong></td>
</tr>
<tr>
<td><strong>Dutasteride group (n = 3.268)</strong></td>
</tr>
<tr>
<td>Incidence all PCa</td>
</tr>
<tr>
<td>Incidence PCa Gleason score 7–10</td>
</tr>
<tr>
<td><strong>Placebo group (n = 3.377)</strong></td>
</tr>
<tr>
<td>Incidence all PCa</td>
</tr>
<tr>
<td>Incidence PCa Gleason score 7–10</td>
</tr>
</tbody>
</table>

PCA = prostate cancer; PSA = prostate-specific antigen; REDUCE = Reduction by Dutasteride of Prostate Cancer Events trial.
very little doubt that the answer to our first question should be positive: Yes, men who have a rising PSA in this setting should be biopsied.

Referring to our case, obviously the appropriate steps were taken. Dutasteride was initiated after an initial negative biopsy. Looking back at the PSA data, a slow rise was observed to start 3.5 yr later, and after confirmation a repeat biopsy was taken 5 yr after the first one. This eight-core biopsy again did not show PCa. This raises the question of appropriate next steps that should take into account the possibility of a transition zone carcinoma as was found in our patient. Saturation biopsies are an obvious option. In our case, with the availability of an expert centre, an MRI imaging centre, and the availability of MRI-guided biopsies, the diagnosis of a Gleason 3 + 4 prostate transition zone cancer was established that seemed to be limited to the prostate. MRI-guided biopsy of tumour-suspicious regions is an accurate method to detect clinically significant PCa in men with repeat negative biopsies and increased PSA. The tumour detection rate of multimodal 3T MRI-guided biopsy was 59% in patients with two or more previous negative TRUS biopsy sessions [9]. Ventral tumours in the transition zone especially are detected, which most often are missed with TRUS biopsy, as was the case in our patient. Furthermore, DWI 3T MRI has high discriminatory performance in separating lesions with low-, intermediate- and high-grade cancer. As illustrated by our case, tumours with a major Gleason 4 component in particular can be recognised [10].

3.2. What if prostate-specific antigen does not rise with dutasteride treatment in men with a previous negative biopsy?

To answer this question we again refer back to the data presented in Andriole et al. [6] and summarised in Table 2. For the detection of Gleason 7–10 PCa, a highly significant difference in the areas under the curve (AUCs) for the change in PSA between the dutasteride-treated men (AUC: 0.699) and the placebo-treated men (AUC: 0.593) was observed in Andriole et al. [6], suggesting that the change in PSA might be the selective indicator for a biopsy when using dutasteride. However, although it is extremely attractive to save 2330 of the total of 3268 biopsies (71.3%), very few clinicians would accept missing 93 of 217 potentially aggressive cancers (42.9%) that can be detected in this population. It seems that unless we can identify other factors that can help us apply biopsies selectively, if we wish to identify all aggressive cancers, there is no other way than biopsying all men as the authors state. This would be for the price of also identifying insignificant PCa in 67.6% of all detected cases [6], however. MR imaging may avoid unnecessary biopsies if its sensitivity to detect Gleason 7–10 disease can be confirmed to be sufficiently high in this setting and if the capacity could be made available to carry out this study in 71% of all men treated with dutasteride who likely will not show a rise in PSA.

A question that is not answered and cannot be answered from the data provided is whether the diagnosis of the 93 cases without an increase of PSA could be safely delayed until a rise in PSA occurs and the same biopsy indication develops as in those men who do show a rise during the 4-yr study period. The very high proportion of clinically insignificant disease, according to the Epstein criteria, which amounts to 67.6% and 49.3% in those who have no PSA increase versus those who have a PSA increase [6], respectively, suggests a very significant number of overdiagnoses that would be another reason to exhaust all possibilities of further risk stratification to avoid unnecessary biopsies.

If we decide to identify all aggressive cancers by biopsying all men using a 2-yr interval, the question remains if the benefits of dutasteride remain favourable in comparison with current clinical follow-up of men with negative biopsies. Dutasteride has obvious potential benefits. Its use significantly reduces the relative risk of positive biopsies, the risk of acute urinary retention, the need for surgery related to BPH, and urinary tract infection [5]. However, due to the protocol of the REDUCE trial that indicated 10 core biopsies were carried out after 2 and 4 yr, PCa was detected in 19.9% of all men after 4 yr, of which, according to the Epstein criteria, 67.6% were classified with insignificant disease. It is obvious that this very high detection rate and large proportion of clinically insignificant disease compare unfavourably with the follow-up of men with negative prostate biopsies in current clinical practice. Therefore, it is too early to conclude that the use of dutasteride will result in a favourable effect on the PCa incidence when applied in a clinical situation.

3.3. Are there other ways to avoid the need to diagnose 93 aggressive cancers except by carrying out 2328 biopsies?

It would help to find a matching reference population with a longer follow-up than 4 yr that is comparable. However, such a population does not seem to be available. Knowledge of the features of PCa treated within the REDUCE trial by radical prostatectomy might give an indication whether follow-up could have been extended to allow diagnosis one or several years later in a still curable state.

Furthermore, one could settle for a cut-off of PSA increase or final PSA that would identify most of the Gleason 7–10 cases of PCa. Unfortunately, none of the sensitivity values of PSA change in Table 2 of Andriole et al. [6] comes into a clinically useful range. The highest proportion of PCa detected with a cut-off of 0.1 for change of PSA over time is 57.1%, which is reciprocal to the 42.9%, or 93 cancers missed because of no rise of PSA. Considering again the sensitivity column in Table 2 in Andriole et al. [6], a cut-off point for change in PSA from month 6 to final PSA of 1.0 or 2.0 ng/ml would still miss 69.1% and 80.2% of the aggressive cancers, respectively (false-negative rate calculated from sensitivities). The PPVs given for cut-off values of final PSA allow the calculation of the number of biopsies that could be saved by missing these cancers. If we would choose a final PSA cut-off of 6 as in our case, we would miss 80.5% of Gleason 7–10 PCa. The available test characteristics clearly also contribute little to a more effective detection of cases of
Gleason 7–10 PCa. What else could be done to improve detection of Gleason 7–10 cancers without rising PSA? It would help to collect more prognostic factors and risk indicators. It is likely that a large proportion of the cancers have been treated by radical prostatectomy. The histologic details of those samples might contribute to a design of more selective procedures as previously mentioned. Once again, multimodal MRI may become an option if the conditions outlined here can be met. Also, earlier work on risk stratification of screen-detected cancers [11] could be applied. The work referred to uses the Prostate Cancer Research Foundation/European Randomised Study of Screening for Prostate Cancer risk calculator (www.prostatecancer-riskcalculator.com) to identify the probabilities of cancer detection in relation to the presence of aggressive and indolent cancers. The additional information needed for such an evaluation would include the outcome of the DRE, prostatic volume, and the presence or absence of a hypoechogenic lesion on TRUS (this last parameter has the smallest impact in the risk assessment). The results of this analysis could be used to prepare a decision tool that could provide informed choices for colleagues and potential patients. The impressive number of 2328 biopsies needed to identify aggressive cancers in 4% of these men may convince some involved in the decision process to delay biopsies in spite of the lack of a proper risk stratification that might show that PCa diagnosed in men without rising PSA are less aggressive and that their diagnosis may be safely delayed.

3.4. Can dutasteride use in men with previous negative biopsies help avoid potentially unnecessary biopsies?

The issue was discussed in the previous section. The conclusion is in line with the conclusion of the authors: Most clinicians and probably most men at risk are likely not to want to miss a 4% probability of diagnosing an aggressive PCa in a potentially curative state. With only slightly more to convince some involved in the decision process to delay biopsies in spite of the lack of a proper risk stratification that might show that PCa diagnosed in men without rising PSA are less aggressive and that their diagnosis may be safely delayed.

4. Conclusions

In men with a previous negative biopsy, dutasteride has the potential to reduce the PCA detection rate, shown in a placebo-controlled trial where a 10-core biopsy was performed after 2 and 4 yr of follow-up independent of PSA values. The high detection rate of aggressive cancers in men on dutasteride who had a rise in PSA indicates that men with any rise in PSA should be biopsied. However, if a rise in PSA will be used as a single biopsy indication in men on dutasteride, >40% of the potentially aggressive cancers might be missed. Because most clinicians do not like to miss this proportion of aggressive PCa in a potentially curative state, selective biopsy indications are needed in men without a rise in PSA. Therefore, additional information and the development of multivariate risk stratification is useful in order not to biopsy all men who use dutasteride. If these risk stratifications will not become available, and clinicians start to biopsy all men who use dutasteride, the benefits of dutasteride are likely to be reduced in comparison with current clinical practice by an excessive number of overdiaognoses.

Author contributions: Pim J. van Leeuwen 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: van Leeuwen, Schröder.

Acquisition of data: van Leeuwen, Kößle, Huland, Hambrock, Barentsz, Schröder.

Analysis and interpretation of data: van Leeuwen, Schröder.

Drafting of the manuscript: van Leeuwen, Schröder.

Critical revision of the manuscript for important intellectual content: Kößle, Huland, Hambrock, Barentsz.

Statistical analysis: van Leeuwen.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Schröder.

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 (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: F.H. Schröder is an advisor to Glaxo Smith Kline, Ferring, and Schering.

Funding/Support and role of the sponsor: None.

References


