available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Prostate Cancer Antigen 3 Score Accurately Predicts Tumour Volume and Might Help in Selecting Prostate Cancer Patients for Active Surveillance

Guillaume Ploussard [*,a,c,1], *Xavier Durand* [a,c,1], *Evanguelos Xylinas* [a,c], *Stéphane Moutereau* [a,c], *Camélia Radulescu* [a], *Aurélien Forgue* [b], *Nathalie Nicolaiew* [c], *Stéphane Terry* [c], *Yves Allory* [a,c], *Sylvain Loric* [a,c], *Laurent Salomon* [a,c], *Francis Vacherot* [c], *Alexandre de la Taille* [a,c]

[a] *Department of Urology, Pathology and Biochemistry, CHU Henri Mondor, APHP, Créteil, France*
[b] *Department of Urology, CHU Bordeaux, Bordeaux, France*
[c] *INSERM U955 Equipe 7, Université Paris Val-de-Marne, Créteil, France*

Article info

Article history:
Accepted November 30, 2010
Published online ahead of print on December 8, 2010

Keywords:
Prostate cancer
Active surveillance
Prostate cancer antigen 3
Low risk
Radical prostatectomy
Insignificant

Abstract

Background: The optimal selection of prostate cancer (PCa) patients for active surveillance (AS) is currently being debated.
Objective: To assess the impact of urinary prostate cancer antigen 3 (PCA3) score as an AS criterion instead of and in addition to the current criteria.
Design, setting, and participants: We prospectively studied 106 consecutive low-risk PCa patients (prostate-specific antigen [PSA] $\leq$10 ng/ml, clinical stage T1c–T2a, and biopsy Gleason score 6) who underwent a PCA3 urine test before radical prostatectomy (RP).
Measurements: Performance of AS criteria (biopsy criteria, PCA3 score, PSA density, and magnetic resonance imaging [MRI] findings) was tested in predicting four prognostic pathologic findings in RP specimens: (1) pT3–4 disease; (2) overall unfavourable disease (OUD) defined by pT3–4 disease and/or pathologic primary Gleason pattern 4; (3) tumour volume $<$0.5 cm^3; and (4) insignificant PCa.
Results and limitations: The PCA3 score was strongly correlated with the tumour volume in a linear regression analysis ($p < 0.001$, r = 0.409). The risk of having a cancer $\geq$0.5 cm^3 and a significant PCa was increased three-fold in men with a PCA3 score of $\geq$25 compared with men with a PCA3 score of $<$25 with most AS biopsy criteria used. There was a trend towards higher PCA3 scores in patients with unfavourable and non–organ-confined disease and Gleason $>$6 cancers. In a multivariate analysis taking into account each AS criterion, a high PCA3 score ($\geq$25) was an important predictive factor for tumour volume $\geq$0.5 cm^3 (odds ratio [OR]: 5.4; $p = 0.010$) and significant PCa (OR: 12.7; $p = 0.003$). Biopsy criteria and MRI findings were significantly associated with OUD (OR: 3.9 and 5.0, respectively; $p = 0.030$ and $p = 0.025$, respectively).
Conclusions: PCA3 score may be a useful marker to improve the selection for AS in addition to the current AS criteria. With a predictive cut-off of 25, PCA3 score is strongly indicative for tumour volume and insignificant PCa.

[1] These authors contributed equally to this work.
* Corresponding author. INSERM U955 Eq07 Department of Urology, CHU Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94000 Créteil, France. Tel. +33149812254; Fax: +33149812568.
E-mail address: g.ploussard@gmail.com (G. Ploussard).

1. Introduction

Active surveillance (AS) is a strategy for managing patients expectantly with the intention to treat if signs of progression emerge [1,2]. Nomograms predicting insignificant prostate cancer (PCa) have been developed, validated, and updated [3]. However, some men are classified with indolent disease although they have truly significant cancer [4,5]. Published AS series have used different criteria, largely based on centre experiences, with no hard data. The most common AS criteria are Gleason score $\leq$6, prostate-specific antigen (PSA) $\leq$10 ng/ml, and clinical stage T1–T2a disease [6–8]. The most stringent AS criteria have recently been reported in a French prospective trial including patients with a tumour length per core of $<$3 mm in fewer than three cores [9]. Studies comparing entry criteria for AS protocols emphasised the risk of misclassification and the limitations of currently available AS criteria [4,10]. Recent studies of repeat biopsies in men under AS have emphasised the risk of encountering upgraded and/or upstaged disease on the second pathologic assessment [11,12]. The inclusion of patients in AS protocols emphasises the necessity of perfectly accurate staging strategies. To date, a limited number of studies have assessed the yield of PCA3 in AS protocols [13]. Although the PCA3 score has become an increasing diagnostic tool for the selection of biopsy candidates, this predictive value has not been thoroughly assessed among PCa patients eligible for AS or for the characterisation of low-volume PCa [14–16].

In this paper, we aimed to assess, in a prospective study, the impact of urinary PCA3 score in predicting the pathologic findings after radical prostatectomy (RP) in low-risk PCa patients and to determine selection value instead of or in addition to the current AS biopsy criteria.

2. Materials and methods

2.1. Patient cohort

Between February 2009 and June 2010, 106 low-risk PCa patients who underwent RP for localised PCa at two French urological centres (Créteil, Bordeaux) were tested for urinary PCA3 score before surgery. The biopsy core number depended on the institution and was comparable for all patients from the same centre. Low-risk PCa was defined as PSA $\leq$10 ng/ml, clinical stage T1c–T2a, and biopsy Gleason score 6. Clinicopathologic parameters were collected in a prospective manner. Each magnetic resonance imaging (MRI) examination was performed at least 6 wk after the prostate biopsies. MRI studies were performed on a 1.5-T whole-body magnetic resonance scanner using a balloon-design endorectal coil inflated with 80 ml of air. Conventional T2-weighted fast-spin echo images were obtained in three orthogonal planes and 3-mm slice thickness.

All RP specimens were evaluated by the same genitourinary pathologist. Briefly, the gland was fixed in 10% formalin, paraffin embedded, and sectioned at 3-mm intervals before whole sections were mounted on slides. A complete sampling procedure was performed. The apical portion, the basis, and the neck of the prostate were separated from the rest of the gland and sampled with a cone technique. Tumours were graded using the Gleason grading system (International Society of Urological Pathology revised version) and staged using the TNM classification. Each focus was outlined on the histologic slices, and volume was determined using the following formula: 0.4 $\times$ length $\times$ width $\times$ cross-section thickness. This estimation has been previously validated [17]. The total tumour volume was obtained by adding volumes of the three most important cancer foci involving the prostate.

2.2. Prostate cancer antigen 3 urine test

First-catch urine specimens were immediately collected after attentive digital rectal examination (DRE), consisting of three strokes on each prostatic lobe, and were stored in a Progensa urine specimen transport kit. Collection was performed the day before RP. Interval between biopsies and RP was at least 3 mo. PCA3 and PSA messenger RNA (mRNA) were isolated using a capture oligonucleotide amplified by the transcription-mediated amplification process and then measured with the Progensa hybridization protection assay. The PCA3 score was calculated as the ratio between PCA3 mRNA and PSA mRNA and was considered relatively constant in normal and cancerous prostate cells.

2.3. Study end point

We assessed the performance of AS criteria in predicting four prognostic pathologic findings in RP specimens: (1) pT3–pT4 disease; (2) overall unfavourable disease (OUD), defined by pT3–4 disease and/or pathologic primary Gleason pattern 4; (3) tumour volume $<$0.5 cm^3; and (4) insignificant PCa. Insignificant PCa was defined by the Epstein criteria as organ confined, no Gleason pattern 4 or 5, and tumour volume $<$0.5 cm^3 [18]. In univariate and multivariate models, we tested the following AS criteria: (1) $<$33% of positive cores; (2) fewer than three positive cores; (3) fewer than three positive cores and $<$3 mm of cancer involvement per core; (4) PCA3 score with four cut-offs ($<$25, $<$35, $<$50, and $<$80); (5) PSA density $<$0.15 ng/ml per gram; and (6) T1–2 disease on MRI findings. PSA density is a current selection criterion reported in AS programs [19]. We chose to incorporate MRI findings because recent findings suggested that new models that combined clinical and biopsy data with MRI performed better than the clinical models for predicting the probability of insignificant disease in RP specimens [20]. In a secondary analysis, the impact of PCA3 score was evaluated in more restricted cohorts defined by the three different current biopsy criteria previously cited (ie, $<$33% of positive cores, fewer than three positive cores, fewer than three positive cores and $<$3 mm of cancer involvement per core).

2.4. Statistical analyses

Correlations between each AS criterion and the pathologic findings in RP specimens were studied. The qualitative data were tested using a χ^2 test or Fisher exact test as appropriate, and continuous data were tested using the student t test. The Mann-Whitney test was used in the absence of a normal distribution. The most significant biopsy criterion, the most significant PCA3 score cut-off, the PSA density, and the MRI findings were then tested in a multivariate model using a logistic regression. Odds ratios (ORs) were calculated with their 95% confidence intervals. Receiver operating characteristic–derived area under the curve (AUC) estimates was used to quantify the predictive accuracy of the PCA3 score in predicting pathologic findings in RP specimens.

3. Results

3.1. Patient cohort

Clinicobiologic parameters of the low-risk patient cohort are listed in Table 1.