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Original article

Percentage of cancer involvement in positive cores can predict unfavorable disease in men with low-risk prostate cancer but eligible for the prostate cancer international: Active surveillance criteria

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Abstract

Objectives: To identify predictive factors of unfavorable disease and of biochemical failure in patients treated with radical prostatectomy but eligible for active surveillance (AS) according to Prostate Cancer Research International: Active Surveillance (PRIAS) criteria. We aimed to introduce and validate the percentage of cancer involvement in positive cores (CIPC) as potential worse predictive factor.

Methods: From January 2002 to December 2007, 750 consecutive subjects underwent radical prostatectomy at a single institution. We identified 147 (19.05%) patients who were eligible for AS based on PRIAS criteria: clinical stage T1c or T2 disease, prostate-specific antigen level of $\leq$10 ng/ml, Gleason score $\leq$6, prostate-specific antigen-D of $<$0.2 ng/ml^2, and fewer than 3 positive biopsy cores. CIPC was included in the analysis.

Results: Of the 147 patients, 95 (66.43%) patients had favorable disease, whereas 48 (33.57%) had unfavorable disease. In multivariate logistic regression, maximum cancer length (odds ratio 12.52, $P < 0.01$) and CIPC (odds ratio 1.70, $P < 0.01$) represented independent predictors of unfavorable prostate cancer. The area under the receiver operating characteristics curve analysis revealed significantly higher performance after including CIPC to the PRIAS criteria (0.61 vs. 0.94, $P < 0.01$). A cutoff of 0.4 mm of CIPC was set to predict unfavorable disease with 93% specificity, 76% sensibility, and 87% accuracy based on the receiver operating characteristics curve analysis. Finally, the 3- and 5-years biochemical recurrence (BCR)-free survival were significantly lower in subjects with CIPC $\geq$0.4 mm, 88.4 % and 81.0% vs. 97.8% and 95.7%, respectively ($P < 0.01$).

Conclusions: Our findings suggest that the inclusion of CIPC to the prostate biopsy features could be helpful to avoid misclassification in patients eligible for AS according to the PRIAS criteria.

Keywords: Active surveillance; PRIAS; Cancer involvement; Radical prostatectomy

1. Introduction

As reported by 2 recently published randomized controlled trials, the diffusion of the screening of the prostate cancer (PCa) with prostate-specific antigen (PSA) testing has reduced the number of PCa deaths [1,2]. Nevertheless, it resulted in a significant increase of overdiagnosis in patients with low-risk PCa, who could not benefit from definitive treatment. To this regard, active surveillance (AS) has gained popularity with the intention of avoiding or postponing interventions in subjects with PCa of low biological potential [3]. Unfortunately, despite the diffusion of various criteria for selecting subjects eligible for AS, several doubts still remain about the ability of these methods in predicting insignificant cancer. In addition, variations in such criteria may result in missing unfavorable PCa and in limiting information about pathological characteristics of the tumors. Criticisms against AS criteria could concern the relevant proportion of upstaging, upgrading, or unfavorable cancer in subjects with apparently low- or favorable-risk PCa [4,5]. According to a recent comparison

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of several contemporary protocols, the Prostate Cancer Research International: Active Surveillance (PRIAS) study showed the highest ability to identify patients with organ-confined low-grade cancer, with an area under the receiver operating characteristics curve (AUC) of 0.62 [6]. Moreover, the number of positive cores (2 cores compared with 1 core) and PSA density (PSA-D) are also shown to be associated with the likelihood of switching to active therapy during follow-up [7]. As concerning the pathological characteristics of patients eligible for AS, the detailed histological features of the positive biopsy are considered essentials as possible factors that could predict disease outcomes. It has been recently reported that cancer length, considered as cumulative cancer length (CCL), and the number of biopsy cores could be useful in predicting insignificant cancer [8].

The aim of this study was to identify predictive factors of unfavorable disease and biochemical failure in patients who underwent radical prostatectomy (RP) but eligible for AS according to the PRIAS criteria. We further aimed to introduce and validate a new variable by incorporating the percentage of cancer involvement in positive cores (CIPC) to the clinical and pathological features of these subjects and to estimate its ability in predicting unfavorable disease and BCR.

2. Patients and methods

From January 2002 to December 2007, 750 consecutive subjects underwent radical retropubic prostatectomy using open or laparoscopic techniques at our institution. All patients underwent clinical evaluation including digital rectal examination, serum PSA level measurement, and transrectal ultrasound. We selected patients who were eligible for AS based on the PRIAS criteria: clinical stage T1c or T2 disease, PSA level of ≤ 10 ng/ml, Gleason score ≤ 6, PSA-D of < 0.2 ng/ml^2, and 1 or 2 positive biopsy cores. Patients with < 10 cores taken at biopsy, neoadjuvant hormonal therapy, insufficient histopathological report, and missing clinical data were excluded. All transperineal prostatic biopsies and RPs were performed at the same institution and RP specimens were evaluated by senior uropathologists. All prostate biopsies were performed with the same technique and by the use of an 18-G needle (cutting length 23 mm).

We recorded data from clinical evaluation (i.e., clinical stage, PSA level, PSA-D, and total prostate volume), from prostatic biopsy (i.e., Gleason score, total number of biopsy cores, maximum cancer length in the positive cores, and total length of positive cores), and from RP specimens (i.e., Gleason score, extracapsular extension, seminal vesicle invasion, and positive surgical margins [PSMs]). Maximum cancer length in a core was defined as the longest length of continuous cancer lesion without gap of benign tissue in a given biopsy session. We incorporated a new detailed histological parameter, the percentage of CIPC, calculated by dividing the CCL to the cumulative length of positive cores (CLPC). CCL was defined as the sum of the length of all cancerous lesions in millimeter, whereas CLPC was defined as the sum of the length of all positive cores in millimeter.

Unfavorable disease was considered as nonorgan-confined disease (pathological stage $>$ pT2) or upgraded disease (Gleason score > 6) or both in the RP specimens as reported by previous reports [9].

Postoperative evaluation included physical examination and PSA level measurement usually performed every 3 months for the first 2 years and every 6 months thereafter. BCR was defined as PSA ≥ 0.2 ng/ml.

The protocol was approved by the internal institutional review board and an informed written consent was obtained from each man before initiation of the study.

2.1. Statistical analysis

All statistical analyses were completed using SPSS v. 19 software (SPSS Inc, IBM Corp, Somers, NY). The qualitative data were tested using the chi-square test or Fisher exact test as appropriate and the continuous variables, presented as median, were tested by Mann-Whitney *U*-test. Univariate and multivariate logistic regression analyses were carried out to identify variables for predicting unfavorable disease from preoperative variables, including age, PSA levels, clinical T stage, prostate volume, number of biopsy cores, biopsy Gleason score, maximum cancer length in a core, CCL, and CLPC. Predictive accuracy of the model was assessed in term of the AUC value, incorporating all significant and independent predictors. AUC values were also calculated by applying the PRIAS criteria to the study cohort. The areas under the curve were compared via the Mantel-Haenszel test. BCR-free survival (BFS) was determined using the Kaplan-Meier method. The significance of the clinical and pathological variables associated with BFS was assessed using the Cox proportional hazards regression model. Curves were tested with the log-rank test. For all statistical comparisons significance was considered as $P < 0.05$.

3. Results

Of all subjects analyzed, 143 (19.05%) fulfilled the PRIAS criteria. Among them, 95 (66.43%) had favorable (Group A) and 48 (33.57%) had unfavorable disease (Group B). Table 1 shows clinical and pathological outcomes of both groups. In terms of PSA level, PSA-D, clinical stage, prostate volume, and mean lengths of individual cores, no difference was observed between both groups. When considering the biopsy histological features, maximum tumor length, CCL, CLPC, and CIPC were significantly higher in Group B than in Group A ($P < 0.01$) (Table 1).