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Original article

What is the optimal definition of misclassification in patients with very low-risk prostate cancer eligible for active surveillance? Results from a multi-institutional series

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Abstract

Background: The risk of unfavorable prostate cancer in active surveillance (AS) candidates is nonnegligible. However, what represents an adverse pathologic outcome in this setting is unknown. We aimed at assessing the optimal definition of misclassification and its effect on recurrence in AS candidates treated with radical prostatectomy (RP).

Materials and methods: Overall, 1,710 patients eligible for AS according to Prostate Cancer Research International: Active Surveillance criteria treated with RP between 2000 and 2013 at 3 centers were evaluated. Patients were stratified according to pathology results at RP: organ-confined disease and pathologic Gleason score ≤ 6 (group 1); organ-confined disease and Gleason score $3 + 4$ (group 2); and non–organ-confined disease, Gleason score $\geq 4 + 3$, and nodal invasion (group 3). Biochemical recurrence (BCR) was defined as 2 consecutive prostate-specific antigen (PSA) ≥ 0.2 ng/ml. Kaplan-Meier curves assessed time to BCR. Multivariable Cox regression analyses tested the association between pathologic features and BCR. Multivariable logistic regression analyses identified the predictors of adverse pathologic characteristics.

Results: Overall, 926 (54.2%), 653 (33.0%), and 220 (12.9%) patients were categorized in groups 1, 2, and 3, respectively. Median follow-up was 32.2 months. The 5-year BCR-free survival rate was 94.2%. Patients in group 3 had lower BCR-free survival rates compared with those in group 1 (79.1% vs. 97.0%, $P < 0.001$). No differences were observed between patients included in group 1 vs. group 2 (97.0% vs. 94.7%, $P = 0.1$). These results were confirmed at multivariable analyses and after stratification according to margin status. Older age and PSA density ≥ 10 ng/ml/ml were associated with higher risk of unfavorable pathologic characteristics (i.e., inclusion in group 3; all $P < 0.001$).

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Conclusions: Among patients eligible for AS treated with RP, only men with Gleason score $\geq 4 + 3$ or non–organ-confined disease at final pathology were at increased risk of BCR. These individuals represent the real misclassified AS patients, who can be predicted based on older age and higher PSA density.

Keywords: Prostate cancer; Active surveillance; Radical prostatectomy; Biochemical recurrence; Oncologic outcomes

1. Introduction

Over the past decades, the introduction of prostate-specific antigen (PSA) screening and early detection programs resulted in a substantial increase in the proportion of patients presenting with low-risk prostate cancer (PCa) [1,2]. These men are usually considered as affected by diseases with a protracted and relatively indolent natural history. For this reason, the oncologic efficacy of curative-intent treatments in selected patients presenting with low-risk tumors has been questioned [3]. Active surveillance (AS) has been proposed in individuals with more favorable PCa to decrease the risk of overtreatment and treatment-related side effects without losing the chance of cure [4,5]. Although ongoing AS protocols adopt stringent inclusion criteria [4], the risk of unfavorable pathologic characteristics at radical prostatectomy (RP) (namely, misclassification) is not negligible [6]. However, what represents the optimal definition of misclassification in this setting is currently unknown [7–9]. Moreover, it is not clear if such misclassification would lead to worse cancer control rates when patients are treated with curative intent. This is key, as the correct knowledge of all pathologic features negatively associated with cancer management outcomes would help establish uniform criteria for AS adoption and discontinuation. In this light, we aimed at identifying predictors of unfavorable disease at final pathology in a large contemporary multi-institutional cohort of patients eligible for AS and treated with RP. Subsequently, we sought to assess the effect of unfavorable characteristics on the risk of biochemical recurrence (BCR) after surgery. We hypothesized that, although the risk of misclassification among AS candidates is substantial, not all the misclassified AS candidates share the same risk of recurrence after RP.

2. Materials and methods

2.1. Study population

After Institutional Review Board approval, 2,832 consecutive patients with histologically confirmed PCa treated with RP or pelvic lymph node dissection or both between 2000 and 2013 at 3 European tertiary referral centers (IRCCS Ospedale San Raffaele, Milan, Italy; Saint-Louis Hospital, Paris, France; and Martini-Clinic, Prostate Cancer Center Hamburg-Eppendorf, Germany) were identified. All patients included in the study were eligible for AS according to the Prostate Cancer Research International: Active Surveillance (PRIAS) criteria [10]: T1c/T2 disease, PSA level ≤ 10 ng/ml, PSA density (PSAD) < 0.2 ng/ml/ml, biopsy Gleason score $3 + 3$, and 1 or 2 positive biopsy cores. None of the patients included in our cohort were enrolled in AS protocols. Exclusion criteria consisted of < 10 biopsy cores at initial biopsy ($n = 1{,}122$). This resulted in a final population of 1,710 patients.

2.2. Covariates and end points

All patients included in the study underwent transrectal ultrasound-guided biopsies, and pathologic specimens were processed by senior uropathologists without central review [11]. All patients had complete clinical and pathologic data, including age, year of surgery, preoperative PSA, PSAD, clinical stage, biopsy Gleason score, number of biopsy cores, number of positive cores, pathologic stage, pathologic Gleason score, surgical margin status, and lymph node invasion (LNI). The TNM stage was applied according to the 2002 American Joint Committee on Cancer staging system for PCa. Patients were then categorized in 3 groups according to pathologic features at RP: (i) men with organ-confined disease and pathologic Gleason score ≤ 6 (group 1), (ii) men with organ-confined disease and pathologic Gleason score $3 + 4$ (group 2), and (iii) patients with non–organ-confined disease or pathologic Gleason score $\geq 4 + 3$ (group 3). Main end point was BCR after RP, which was defined as 2 consecutive PSA values ≥ 0.2 ng/ml after RP. Time to BCR was calculated as the one from RP to the occurrence of BCR or last follow-up.

2.3. Statistical analyses

Medians and interquartile ranges were reported for non–normally distributed continuous variables. Frequencies and proportions were reported for categorical variables. The Kruskal-Wallis and chi-square tests were used to compare medians and proportions between groups 1, 2, and 3.

Our statistical analyses consisted of several steps. First, PSAD was dichotomized according to the most informative cutoff predicting unfavorable disease. Multivariable logistic regression analyses were performed to assess the association between preoperative characteristics and the risk of non–organ-confined disease; positive surgical margins; pathologic Gleason score $3 + 4$, $\geq 3 + 4$, and $\geq 4 + 3$; and unfavorable PCa (i.e., inclusion in group 3). Multivariable Cox regression analyses assessed the effect of preoperative variables on the risk of BCR. Second, Kaplan-Meier analyses