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Prostate Cancer

Adverse Pathologic Features at Radical Prostatectomy: Effect of Preoperative Risk on Oncologic Outcomes

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Abstract

Background: Up to 30% of patients with low-risk prostate cancer (PCa) are found to have features of aggressive disease at radical prostatectomy (RP). Several predictive nomograms and novel genomic markers have been developed to estimate the risk of adverse pathology in men eligible for active surveillance (AS). However, oncologic risk associated with these findings remains unknown.
Objective: To determine if the presence of adverse pathologic features at RP in patients eligible for AS is prognostic of poor oncologic outcome independent of pretreatment risk status.
Design, setting, and participants: A total of 2660 patients underwent immediate RP at our institution between 1998 and 2008. Patients were stratified as low, intermediate, or high risk according to the D'Amico clinical risk criteria.
Outcome measurements and statistical analysis: The rates of adverse pathology were reported, and the 5-yr risk of biochemical recurrence (BCR) was calculated in the presence of aggressive disease.
Results and limitations: The 5-yr risk of BCR in patients with extracapsular extension (n = 937) was 43% (95% confidence interval [CI], 40–46) overall but only 15% (95% CI, 11–22) for those who met the criteria for low risk (n = 181). For the 473 patients with pathologic Gleason score 4 + 3, the risk of recurrence at 5 yr was 41% (95% CI, 37–46) overall, 13% (95% CI, 5–27) for low-risk men (n = 41), 41% (95% CI, 35–47) for intermediate-risk men (n = 287), and 51% (95% CI, 43–60) for high-risk men (n = 145). Limitations include use of BCR as the study end point and surrogate for oncologic outcome in men who received curative treatment.
Conclusions: The presence of pathologically unfavorable disease in patients eligible for AS is not informative as to the safety of this treatment modality. We question the relevance of adverse pathology as the end point for predictive tools designed to guide treatment decisions in low-risk PCa.
Patient summary: The risk of biochemical recurrence associated with adverse pathologic findings at prostatectomy is reduced by approximately 50% in men with clinically low-risk prostate cancer.

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1. Introduction

Widespread use of prostate-specific antigen (PSA) as a primary screening tool for prostate cancer (PCa) has led to the increased detection of clinically insignificant tumors. It is estimated that up to 60% of men diagnosed by PSA screening have low-risk PCa [1], yet most of these men undergo invasive treatment involving surgery or radiotherapy

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[2,3]. Such interventions carry a non-negligible risk of urinary and sexual dysfunction that can adversely affect a man's quality of life.

As clinicians have grown aware of the hazards associated with overdiagnosis and overtreatment of PCa, active surveillance (AS) has emerged as a viable option for the conservative management of low-risk organ-confined disease. The D'Amico classification [4] is the most commonly used criterion for the definition of clinical risk that includes low-risk patients with Gleason scores ≤6, clinical stage T2a or lower, and PSA level ≤10 ng/ml. Such low-risk patients who are found to have low-volume disease on biopsy are offered AS, with close monitoring and the intent of curative treatment at signs of disease progression. Preliminary data from several prospective AS series have shown promising results, with very low rates of disease-specific mortality and moderate rates of intervention in the first few years of surveillance [5,6]. However, definitive conclusions are premature because of the relatively short follow-up times available even in the longest series.

Some investigators have cautioned against overutilizing AS, citing a moderate incidence of pathologically unfavorable disease in patients with low-risk PCa who would have been eligible for AS. Reported rates of Gleason sum upgrading range from 20% to 54% and pathologic upstaging from 6% to 26%, depending on the stringency of the inclusion criteria applied [7–11]. These findings have raised concerns regarding the adequacy of current AS eligibility criteria to differentiate appropriately between candidates for conservative management and those who require definitive treatment.

After examining the incidence of Gleason score upgrading in a low-risk patient population, Kulkarni et al [12] concluded that "caution should be exercised in recommending nonradical therapy to individuals with a high probability of undetected high-grade disease." Similar conclusions were drawn by Isariyawongse et al [13], who found that the risk of upgrading increased with advanced age and advised that "caution should be exercised when recommending active surveillance in older men." To this end, several nomograms have been constructed to predict the probability of pathologic upgrading in patients with low-risk PCa [14,15]. Several novel genomic markers have been developed to predict the risk of disease recurrence and progression in patients who have undergone treatment for PCa [16,17], as well as to better estimate the presence of pathologically unfavorable disease in men eligible for AS and to recommend immediate treatment for those with increased risk of upgrading or upstaging [18].

Such recommendations are based implicitly on the hypothesis that adverse pathology is prognostic of poor oncologic outcome in a manner relatively independent of pretreatment risk status (Fig. 1). An alternative hypothesis is that oncologic risk associated with adverse pathologic features is highly influenced by preoperative risk status (Fig. 2). To evaluate the second hypothesis, we analyzed data from patients with adverse pathologic features at radical prostatectomy (RP), examined the relationship between upstaging/upgrading with biochemical recurrence (BCR) (as a surrogate for oncologic outcome), and investigated the effect of preoperative risk on this relationship.

2. Patients and methods

Following institutional review board approval, we performed a retrospective review of data collected from our PCa database on all patients undergoing immediate RP at Memorial Sloan Kettering Cancer Center (MSKCC) from 1998 to 2008. The final cohort consisted of 2660 patients with complete clinical, pathologic and follow-up data available and who received neither neoadjuvant nor adjuvant therapy following surgery.

Patients were stratified according to the D'Amico risk criteria for BCR based on clinical features: low risk (PSA ≤10 ng/ml, ≤cT2a, and biopsy Gleason ≤6), intermediate risk (PSA >10 and ≤20 ng/ml, cT2b, or biopsy Gleason 7), and high risk (PSA >20 ng/ml, lower than cT2b, or biopsy Gleason ≥8). We chose to use the D'Amico classification because it is the most commonly used criterion for the definition of clinical risk and used at many centers (including MSKCC) for inclusion of patients into AS protocols. The National Comprehensive Care Network recommends AS as an option for men with low-risk disease. We accept that there are a variety of different criteria for AS and many involve characteristics in addition to stage, grade, and PSA such as number of positive cores or percentage of core involvement. As is, our patient cohort constitutes a more diverse group that likely includes men with high-volume disease who at some centers would not be considered for or offered AS. We therefore repeated our analyses using more restrictive definitions of eligibility for AS.

The primary end point of the study was the effect of preoperative risk on BCR in men with adverse pathologic features at RP, defined as the presence of extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node invasion (LNI), or high-grade disease (Gleason sum >3 + 3). BCR was defined as a postoperative PSA elevation ≥0.2 ng/ml with a subsequent confirmatory value.

2.1. Statistical considerations

Univariable and multivariable Cox proportional hazards models were built with time to BCR as the outcome and preoperative risk as the covariate restricted to men with adverse pathologic features. The multivariable model was adjusted for pathologic Gleason scores and the presence of other adverse features (ECE, SVI, and LNI). BCR-free survival was estimated using the Kaplan-Meier method. The log-rank test was used to test differences between groups. All p values were two sided, with $p < 0.05$ considered a significant difference between groups.

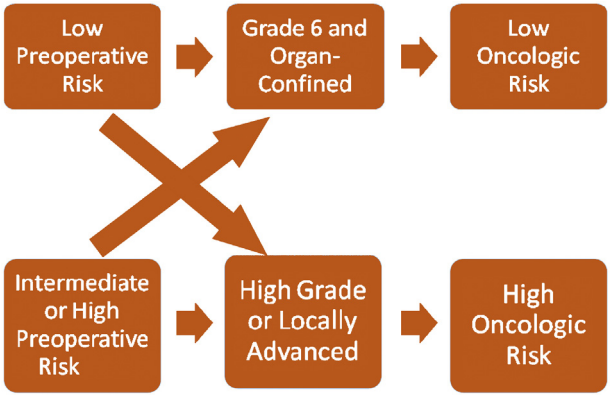

Fig. 1 – Hypothesis 1 implies that the presence of adverse pathologic features is prognostic of poor oncologic outcome relatively independent of pretreatment risk status.