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Prostate Cancer

Adverse Disease Features in Gleason Score 3 + 4 "Favorable Intermediate-Risk" Prostate Cancer: Implications for Active Surveillance

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Abstract

Background: According to a recent National Comprehensive Cancer Network (NCCN) guidelines update, patients with Gleason score (GS) 3 + 4 prostate cancer (PCa) and "favorable intermediate-risk" (FIR) characteristics might be offered active surveillance (AS). However, the risk of unfavorable disease features and its prediction in this subset of patients is not completely understood.
Objective: To identify the risk of unfavorable disease and potential predictors of adverse outcomes among GS 3 + 4 FIR PCa patients.
Design, setting, and participants: The study included patients with biopsy GS 3 + 4 and otherwise fulfilling the NCCN low-risk definition (prostate-specific antigen [PSA] <10 ng/ml, cT2a or lower) undergoing radical prostatectomy (RP) from 2006 to 2014 at a single institution.
Outcome measurements and statistical analysis: Complete information on PSA, PSA density (PSAD), clinical stage, percentage of positive cores, percentage of maximum surface specimen involvement, and RP pathology were available. GS upgrade and downgrade, non–organ-confined and non–specimen-confined disease, unfavorable disease (pT3–T4 and/or pN1 and/or a pGS ≥4 + 3) were the outcomes. Statistical analysis included descriptive statistics and multivariable logistic regression.
Results and limitations: A total of 156 patients (13.1%) experienced GS upgrade; 201 (16.9%) were downgraded. Overall, 205 men (17.2%) harbored non–organ-confined disease, and 295 (24.8%) had unfavorable disease. Age (odds ratio [OR]: 1.06), percentage surface involvement (OR: 1.01), and PSAD (OR: 1.83) were the only significant predictors of upgrade. Age (OR: 1.05), clinical stage (OR: 1.74), percentage of positive cores >50% (OR 1.57), percentage of surface area (OR: 1.02), and perineural invasion (OR: 1.89) were significant predictors of unfavorable disease at RP. The retrospective design is a limitation.
Conclusions: AS is a possible option for a subset of men with FIR GS 3 + 4. However, clinical models alone have a limited role in GS upgrade prediction, and alternative tools warrant further investigation.
Patient summary: Patients with Gleason score 3 + 4 at biopsy, low prostate-specific antigen, and low stage might consider the option of active surveillance, but the use of clinical information alone might be not adequate for thorough risk-adapted counseling.

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1. Introduction

Whether or not active surveillance (AS) should be extended to men with intermediate-risk (IR) prostate cancer (PCa) is a highly debated issue. AS has emerged as a viable option for a considerable number of men to counterbalance the risk of overdiagnosis and overtreatment of clinically indolent disease. Some AS protocols have included a small proportion of men with Gleason score (GS) 7 disease [1,2] and, more recently, National Comprehensive Cancer Network (NCCN) guidelines [3] have listed AS an option for men with "favorable intermediate-risk" (FIR) PCa (GS 3 + 4, percentage of positive cores <50%, and only one additional IR factor). However, most evidence supporting this risk reclassification is indirect [4], and many studies relied on repeated biopsy results rather than on whole-specimen pathology [5], providing a partial perspective of the complete picture. Since its introduction, GS has been regarded as the single most important element in risk assessment [6].

Concerns about undergrading/staging at diagnosis and missing the opportunity for cure if radical intervention is delayed are the main drawbacks to the use of AS in the setting of FIR PCa. Understanding the risk of harboring unfavorable disease among this subgroup may foster more appropriate selection of patients for AS protocols. The aim of this study is to assess the risk of adverse characteristics in men with very favorable risk GS 3 + 4 PCa and to identify potential predictors of unfavorable features.

2. Patients and methods

2.1. Patient selection and evaluation

All patients with biopsy GS 3 + 4, prostate-specific antigen (PSA) <10 ng/ml, and clinical stage cT2a or lower who underwent radical prostatectomy (RP) at our institution between 2006 and 2014 were included in this retrospective cohort analysis. All had a histologically confirmed diagnosis of PCa (transrectal prostate biopsy) within 3 mo before surgery. Due to the referral nature of our practice, a pathologist at our institution reviewed all the biopsy slides. Thus the biopsy GS score reported represents the result of our internal review [7], and detailed biopsy information was available for all of the patients. RP was performed using an open retropubic, laparoscopic, or robot-assisted approach by experienced urologists. Pelvic lymph node dissection was carried out according to the operating surgeons' preferences. Surgical specimens were processed and analyzed using a standardized technique, as previously described [8]. The institutional review board approved the study.

2.2. Data collected

The clinical and biopsy variables included age at surgery, presurgery PSA, PSA density (PSAD), clinical stage, primary and secondary Gleason grading on biopsy, number of positive cores, number of total cores and percentage of positive/total cores, maximum percentage of surface specimen tumor involvement, presence of perineural invasion, and/or high-grade prostatic intraepithelial neoplasia (HGPIN) in biopsy specimens.

Pathologic variables were primary and secondary GS, pT and pN stage, and surgical margin status. American Joint Committee on Cancer TNM 6th edition (2002) was used for pathologic staging, and GS was assigned according to the 2005 International Society of Urological Pathology (ISUP) modified Gleason scoring system [9]. Upgrade was defined as GS ≥4 + 3 at definitive pathology. Patients with advanced pathologic stage (pT3–T4 and/or pN1) and/or a pGS ≥4 + 3 were considered as "unfavorable disease" at RP [10]. Pathologic stage pT2 or lower and N0 was classified as "organ-confined disease," whereas "specimen-confined disease" was pT2–pT3a PCa with negative margins (R0) and negative lymph nodes (pN0) [11].

2.3. Statistical analysis

In addition to descriptive statistics, we used the chi-square test for comparing categorical variables and the Student *t* test or Wilcoxon rank sum test for comparison of continuous variables. Clinical data (age, PSAD, with logarithmic transformation, and clinical stage) and detailed biopsy information were analyzed in multivariable prediction models using logistic regression. The percentage of positive cores/total and percentage of specimen surface tumor involvement were considered both as continuous values and categorized as <50% or ≥50%, in accordance with the cut-off suggested by the recent NCCN guidelines update [3]. All tests were two sided with α value of 0.05.

3. Results

A total of 1190 patients were included. Table 1 shows the baseline demographic and clinical features of the cohort. Median age at surgery was 62 yr (interquartile range [IQR]: 57–67); PSA was 5.2 ng/ml (IQR: 4.3–6.6). The cT stage was T1 in 812 patients (68%) and T2a in 378 (32%). Median percentage of positive cores was 33% (IQR: 19–50), and median surface area percentage of involvement was 25% (IQR: 10–50); perineural invasion was present in 273 patients (23%).

Table 2 lists the pathologic outcomes of the cohort. The pT stage was 2a–2b in 274 (23%), 2c in 723 (61%), 3a in 144 (12%), and 3b in 48 (4%). Pathologic GS was 6 in 17%, 3 + 4 in

Table 1 – Demographic and preoperative features of the Gleason score 3 + 4 very favorable intermediate-risk cohort

	(*n* = 1190)
Age at surgery, yr	
Median (IQR)	62 (57–67)
Range	37–79
Preoperative PSA, ng/ml	
Median (IQR)	5.2 (4.3–6.6)
Clinical T stage (%)	
T1c	812 (68)
T2a	378 (32)
Total biopsy cores	
Median (IQR)	12 (12–14)
Positive biopsy cores	
Median (IQR)	4 (3–6)
Positive cores, %	
Median (IQR)	33 (19–50)
Surface area, %	
Median (IQR)	25 (10–50)
HGPIN (%)	
No	1064 (89)
Yes	126 (11)
Perineural invasion (%)	
No	916 (77)
Yes	274 (23)

HGPIN = high-grade prostatic intraepithelial neoplasia; IQR = interquartile range; PSA = prostate-specific antigen.

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