Original Study

Grade Group Underestimation in Prostate Biopsy: Predictive Factors and Outcomes in Candidates for Active Surveillance

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Abstract

Results from prostate biopsy may differ from the final pathology after radical prostatectomy in one-half of the cases. Underestimation of the Gleason score on the biopsy seems to have consequences on the outcomes. We developed a nomogram to improve risk classification, in order to better counsel patients when several therapeutic options are available.

Objective: We intended to analyze the outcomes and predictive factors for underestimating the prostate cancer (PCa) grade group (GG) from prostate biopsies in a large monocentric cohort of patients treated by minimally invasive radical prostatectomy (RP). **Materials and Methods:** Using a monocentric prospectively maintained database, we included 3062 patients who underwent minimally invasive RP between 2006 and 2013. We explored clinicopathologic features and outcomes associated with a GG upgrade from biopsy to RP. Multivariate logistic regression was used to develop and validate a nomogram to predict upgrading for GG1. **Results:** Biopsy GG was upgraded after RP in 51.5% of cases. Patients upgraded from GG1 to GG2 or GG3 after RP had a longer time to biochemical recurrence than those with GG2 or GG3 respectively, on both biopsy and RP, but a shorter time to biochemical recurrence than those who remained GG1 after RP ($P < .0001$). In multivariate analyses, variables predicting upgrading for GG1 PCa were age ($P = .0014$), abnormal digital rectal examination ($P < .0001$), prostate-specific antigen density ($P < .0001$), percentage of positive cores ($P < .0001$), and body mass index ($P = .037$). A nomogram was generated and validated internally. **Conclusions:** Biopsy grading system is misleading in approximately 50% of cases. Upgrading GG from biopsy to RP may have consequences on clinical outcomes. A nomogram using clinicopathologic features could aid the probability of needing to upgrade GG1 patients at their initial evaluation.

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed solid malignant tumor among men in the United States and Western Europe.[1] In recent years, the widespread use of prostate-specific antigen (PSA) as a diagnostic marker has mainly led to the identification of PCa in patients with low-risk PCa, as defined by the D'Amico criteria.[2] Treatment options are usually decided upon based on PSA level, biopsy Gleason score (GS), and clinical ± radiologic stage. Thus, the GS from prostate biopsy is a crucial factor in the initial evaluation of patients with PCa and can lead to different therapeutic decisions.

However, the GS from a biopsy may be associated with significant grading errors and may differ from the final pathologic result of the specimen.[3] Indeed, 30% to 50% of patients with low-risk disease have their GS upgraded after analysis of the radical prostatectomy (RP) specimen.[4] This is clinically important because the presence of a higher GS is associated with an increased risk of biochemical recurrence and cancer-specific mortality.[5] Furthermore, when active surveillance is decided upon for low-risk PCa, it is mandatory not to miss an aggressive tumor.

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Recently, the International Society of Urological Pathology (ISUP) Consensus Conference proposed a new grading system (Grade Groups [GGs] 1-5) in order to provide more accurate stratification of tumors.[6] The aim of this article was to identify, in a large monocentric cohort, the clinical factors that predict needing to upgrade GG from biopsy to RP specimen, particularly for GG1 patients, and its consequences on outcomes.

Materials and Methods

Study Population

We reviewed our prospectively maintained database for all consecutive patients treated at Institut Mutualiste Montsouris by either laparoscopic or robot-assisted RP between 2006 and 2013. Institutional review board approval was received. The following data were collected from all patients: age at diagnosis, body mass index (BMI), PSA, clinical stage evaluated by digital rectal examination (DRE), prostate size evaluated by transrectal ultrasound, biopsy findings, pathologic findings, and oncologic outcomes. A total of 3062 RPs and corresponding needle biopsies were included in this study.

Grading System

The diagnosis of PCa was assessed by a transrectal ultrasound-guided biopsy. Most patients were operated on within 4 months of the biopsy. Most biopsies were performed at outside institutions, but all biopsy slides were reviewed and regraded at our institution prior to RP. A minimal number of 10 cores was needed for inclusion in the study. Analyses of all needle biopsies and RP specimens were centralized and performed by dedicated genitourinary pathologists. Gleason grading for prostatic carcinoma followed the 2005 ISUP Consensus Conference[7] and was adapted to the new grading system (GGs 1-5).[6] Upgrading and downgrading were defined as an increase or decrease, respectively, from one prognosis group to another.

Statistical Analyses

Quantitative variables were described as their medians (interquartile ranges [IQRs]), and qualitative variables as numbers (percentages). Differences between underestimated patients and nonunderestimated patients were tested using either the χ^2 test for qualitative variables or the Wilcoxon rank-sum test for quantitative variables. The effects of variables were tested in multivariate analyses using a likelihood ratio test. The GG was determined using a logistic regression model that included the regression coefficients of the significant predictive factors in multivariate analysis. This included the following variables: BMI, percentage of positive cores, DRE, PSA density, and age. Because "percentage of positive cores" and "PSA density" were included in the model via cubic splines, no odds ratios are given for these variables. Log-linearity was checked for continuous variables. Non–log-linear variables were considered using cubic splines with 4 knots for percentage of positive cores and 3 knots for PSA density level. Discrimination of the score was evaluated using the area under the receiver operating characteristic curve (AUC). Estimations are given with their 95% confidence intervals (CI) estimated by the bootstrap method. Internal validations were performed using the bootstrap method, and the final AUC estimates were corrected for over-optimism. A calibration plot was generated using boostrapping to get bias-corrected (overfitting-corrected) estimates of predicted versus observed values, based on subsetting predictions on nonparametric smoothers. All tests were 2-sided at the $P = .05$ level. All statistics were performed using R 3.0.1 software.

Results

Clinical and Pathologic Findings

The characteristics of the study population are presented in Table 1. A total of 263 patients (8.6%) were known to have prior negative biopsy. For the rest of the population, Gleason GG was determined from the initial biopsy. The GG from the biopsy was consistent with the specimen in 1323 patients (43.2%) (Table 2).

Table 1 Characteristics of the Study Population

Variable	All Patients (n = 3062)
Median age at diagnosis, y	61.8 [57.7]
Median PSA, ng/mL	6.8 [5.3-9.3]
Median BMI, kg/m^2	25.5 [23.8-27.5]
Clinical stage	
T1c	1952 (63.9)
T2a	813 (26.6)
T2b	188 (6.1)
T2c	89 (2.9)
T3a	15 (0.5)
T3b	1 (0)
Prostate volume, cm^3	50 [40-60]
Prior negative biopsy	263 (8.6)
Number of biopsy cores	12 [10-13]
Median percentage of positive biopsies	25 [16-40]
Unilateral positive biopsies	1772 (57.9)
Grade group from the biopsy	
1	1791 (58.5)
2	811 (26.5)
3	333 (10.9)
4	111 (3.6)
5	16 (0.5)
Grade group from the specimen	
1	721 (23.5)
2	973 (31.8)
3	1235 (40.3)
4	91 (3)
5	42 (1.4)
Pathologic stage	
pT2a	197 (6.4)
pT2b	165 (5.4)
pT2c	1814 (59.3)
pT3a	680 (22.2)
pT3b	205 (6.7)
Surgical positive margin	537 (17.5)

Categorical data are presented as n (%); continuous data as median [IQR].
Abbreviations: IQR = interquartile range; PSA = prostate-specific antigens.