



Original article

Clinical and pathologic predictors of Gleason sum upgrading in patients after radical prostatectomy: Results from a single institution series

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Abstract

Objectives: Preoperative Gleason scores (GSs) are often upgraded after pathologic examination of the prostate following radical prostatectomy (RP). There have been disparate reports of the impact of different factors as predictors of GS upgrading after RP. We sought to study the robustness of frequently reported predictors in an unselected single institution cohort.

Patients and methods: A total of 684 patients with biopsy-proven prostate cancer treated with RP between 2004 and 2007 were included in the study. The association between clinical and pathologic parameters and GS upgrading was retrospectively evaluated. Logistic regression analysis was used to identify predictors of pathologic grading changes. Likelihood of upgrading was compared between tertile groups for prostate volume and prostate-specific antigen (PSA) density using χ^2 analysis and multivariate logistic regression. Pathologic outcomes were compared between cases with and without GS upgrading.

Results: The overall mean age was 64.3 years, with median PSA level of 7.04 ng/ml. Overall, 203 cases (29.7%) were upgraded, whereas 481 patients (70.3%) were downgraded or had identical biopsy and pathologic GS after RP. Patients with prostate volume of <31 g were upgraded in 32.6% of the cases compared with 21.9% in patients with prostate volume of >45 g ($P = 0.020$). On multivariate analysis preoperative PSA ($P < 0.0001$), prostate volume ($P < 0.0001$), and PSA density ($P < 0.0001$) were predictive of Gleason sum upgrading. Upgraded patients were more likely to have extracapsular extension, seminal vesicle invasion, positive surgical margins, and lymphonodular invasion at RP ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively).

Conclusions: Smaller prostate volume and higher PSA level are associated with clinically significant upgrading of GS. PSA density as a function of both is a significant predictor of GS upgrading in low- and high-risk patients. This may be of relevance in the pretreatment risk assessment of prostate cancer patients. © 2009 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Gleason sum; Upgrading; Prostate-specific antigen; PSA density; Prostate volume

1. Introduction

A wide range of treatment options are offered to patients with prostate cancer at present, whereby treatment selection for prostate cancer is greatly based upon risk assessment

derived from Gleason score (GS) in biopsy, prostate-specific antigen (PSA), and clinical stage [1]. GS remains the most accurate variable for predicting prostate cancer aggressiveness [2]. More aggressive PCa at radical prostatectomy (RP) than diagnosis at biopsy is seen in up to 68% of men [3–6]. Therefore, it is important to assess the accuracy of biopsy GS in predicting the actual pathologic status in order to choose the suitable treatment tailored for each patient.

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Several recent studies have evaluated factors that could potentially predict GS upgrading (higher GS category in the RP specimen than in the biopsy) [2,4,7–10]. However, there have been contradictory reports about the ability of the same variables to predict or to fail to predict a greater risk of GS upgrading [4,11–13]. These variables most frequently included PSA level and prostate volume.

The aim of our study was to determine clinical and pathologic factors associated with a change in actual pathologic status in our unselected single institution series, which could be taken into consideration during clinical decision-making, especially in those patients who are candidates for watchful waiting, active surveillance, or brachytherapy, but also in patients with high-risk features on biopsy, which lead to consideration of additional adjuvant therapy in patients undergoing radiotherapy.

2. Patients and methods

2.1. Patient selection and data collection

This was an institutional review board (IRB) approved study. The study comprised 684 patients who underwent open RP with bilateral lymphadenectomy at the Department of Urology of the Ludwig-Maximilians University Munich between 2004 and 2007. Data were analyzed retrospectively. Clinical and pathologic data included preoperative PSA, which was measured before a digital rectal examination (DRE) and transrectal ultrasound (TRUS), body mass index (BMI), GSs in biopsy and RP specimen, prostate volume (measured as the weight of the RP specimen), PSA density, pathologic T stage, extracapsular extension (ECE) rate, positive surgical margin rate, lymphonodular invasion rate, and PSA values at follow-up (range 3–36 mo). For prostate volume we used pathologic prostate weight as a surrogate for preoperative TRUS. It has been shown in several studies that pathologic weight accurately correlates with TRUS volume [14,15]. The biopsy Gleason sum was predominantly assigned by outside institutions or in a small percentage of cases by the Department of Pathology of the Ludwig-Maximilians University Munich. The vast majority

of patients underwent extended biopsy. All RP specimen were processed according to the Stanford protocol and were graded according to the Gleason system by the Department of Pathology [1]. Gleason sum upgrading was defined as a biopsy Gleason sum changing from ≤ 6 to ≥ 7 , from ≥ 7 to a higher Gleason sum, as well as Gleason changing from 3+4 to 4+3.

2.2. Statistical analysis

Continuous variables were compared between Gleason upgrading vs. no upgrading groups using either the two-sample *t*-test or the Wilcoxon rank sum test; categorical variables were compared using the χ^2 test. Univariate logistic regression analysis was performed. Two separate multivariate logistic regression analyses were performed with the backward elimination model selection method to find the best predictors for Gleason upgrading. For multivariate analysis, prostate volume, preoperative PSA values, and PSA density were transformed using the natural logarithm due to a skewed distribution. The first multivariate analysis included age, BMI, PSA (log scale), and prostate volume (log scale) as potential predictors; the second multivariate analysis included age, BMI, and PSA density (log scale) as potential predictors. Two separate analyses were conducted, because PSA density is the quotient of PSA divided by prostate volume. For the analysis in Table 1, prostate volume and PSA density were categorized based on tertiles. χ^2 analysis and multivariate logistic regression analysis adjusting for age and BMI were conducted for the results in Table 1. As for assessing the predictive performances of the observed independent predictors for upgrading, ROC curves have been constructed. Locally weighted regression (LOESS) analysis was used to plot the association between prostate volume and probability of upgrading stratified by Gleason groups and by PSA groups. Kaplan-Meier estimator was used to evaluate biochemical recurrence-free survival with biochemical recurrence defined as PSA greater than or equal to 0.4 ng/ml in patients with GS upgrading vs. patients without GS upgrading [16]. Statistical difference between the upgraded and non-upgraded group was determined using the log rank test. A *P* value < 0.05 was considered significant.

Table 1
The risk of GS upgrading as a function of prostate volume and PSA density

				<i>P</i> value
Prostate volume (g)	<31	31–45	>45	
% of upgrading	32.6	32.3	21.9	0.020
Adjusted OR (95% CI)	1.85 (1.19, 2.87)	1.80 (1.16, 2.80)	Reference	0.011
PSA (ng/ml)	<5.6	5.6–8.9	>8.9	
% of upgrading	24.2	29.8	35.4	0.035
Adjusted OR (95% CI)	Reference	1.33 (0.87, 2.03)	1.67 (1.09, 2.54)	0.060
PSA density (ng/ml/g)	<0.14	0.14–0.23	>0.23	
% of upgrading	17.1	32.6	37.4	<0.001
Adjusted OR (95% CI)	Reference	2.13 (1.46, 3.68)	3.00 (1.90, 4.74)	<0.001

Table 2
Comparison of clinical and pathologic patient characteristics in the GS upgrading group vs. the group without GS upgrading

	No Gleason upgrading	Gleason upgrading	P value
N	481	203	
Age (mean \pm SD)	64.2 \pm 7.0	64.3 \pm 6.6	0.855
BMI (kg/m ²) (mean \pm SD)	26.6 \pm 3.3	26.5 \pm 3.1	0.881
PSA (ng/ml) (median, IQR)	6.7 (4.7, 9.9)	7.8 (5.5, 11.5)	<0.001
Gleason Biopsy (N, %)			0.002
\leq 6	290 (60%)	154 (76%)	
7a (3+4)	109 (23%)	26 (13%)	
7b (4+3)	40 (8%)	11 (5%)	
\geq 8	42 (9%)	12 (6%)	
Prostate volume (g) (median, IQR)	40 (30, 52)	35 (27, 45.3)	0.003
PSA density (ng/ml/g) (median, IQR)	0.17 (0.12, 0.25)	0.22 (0.15, 0.34)	<0.001
Gleason pathology (N, %)			<0.001
\leq 6	368 (76.5%)	0 (0%)	
7a (3+4)	81 (17%)	100 (49%)	
7b (4+3)	20 (4%)	34 (17%)	
\geq 8	12 (2.5%)	69 (34%)	
pTNM (N, %)			<0.001
T1-2	407 (85%)	113 (56%)	
T3-4	74 (15%)	90 (44%)	
ECE rate (N, %)	74 (15%)	90 (44%)	<0.001
SV invasion rate (N, %)	25 (5%)	36 (18%)	<0.001
Positive SM rate (N, %)	63 (13%)	60 (30%)	<0.001
LNI (N, %)	7 (1.5%)	21 (10%)	<0.001

All analyses were performed using SAS 9.1 (SAS, Inc., Cary, NC) and R.2.7.2.

3. Results

The clinical and pathologic characteristics of the patients with and without GS upgrading are shown in Table 2. After RP, the final pathologic GS was upgraded in 203 (29.7%) patients and not upgraded in 481 (70.3%) patients. Most patients (154, 76%) in the GS upgrading group had a biopsy GS \leq 6. Patients of both groups were similar in age (median age of 64.3 and 64.2, respectively) and BMI (26.5 vs. 26.6; $P = 0.881$). The upgraded group had a significantly higher preoperative PSA level ($P < 0.001$), smaller prostate volume ($P = 0.003$), higher PSA density ($P < 0.001$), and lower Gleason biopsy score ($P < 0.001$) (Table 2).

In univariate logistic regression analyses of potential preoperative predictors for GS upgrading, prostate volume (log) ($P = 0.0018$), preoperative PSA level (log) ($P < 0.0001$), and PSA density (log) (<0.0001) were statistically significant contributors to GS upgrading with a relative risk of 0.537 (95% CI 0.363, 0.794), 1.691 (95% CI 1.339, 2.137), and 1.943 (95% CI 1.524, 2.477), respectively (Table 3).

In multivariate logistic regression analysis, the best predictors among age, BMI, preoperative PSA, and prostate volume of GS upgrading obtained by the backward elimination selection procedure including all the patients of both groups were preoperative PSA level (log) ($P < 0.0001$) and prostate volume (log) ($P < 0.0001$) with a relative risk of 1.826 (95% CI 1.410, 2.366) and 0.403 (95% CI 0.265,

0.612), respectively. The same analysis with age, BMI and PSA density revealed PSA density (log) ($P < 0.0001$) as strongest independent predictor for upgrading of GS with a relative risk of 1.956 (95% CI 1.533, 2.495). Table 1 shows the risk of GS upgrading as a function of prostate volume and PSA density, each divided into tertiles. PSA level as categorical variable failed to be a significant predictor of GS upgrading. Patients with prostate volume <31 g were upgraded in 32.6% of the cases compared with 21.9% in patients with prostate volume > 45 g ($P = 0.020$). Patients with PSA < 5.6 ng/ml showed Gleason upgrading in 24.2% of cases, as opposed to 35.4% in patients with PSA > 8.9 ng/ml ($P = 0.035$). Patients with a PSA density < 0.14 ng/ml/g showed Gleason upgrading in 17.1% of cases compared with 35% in patients with PSA density > 0.14 ng/ml/g ($P < 0.001$) (Table 1).

As for assessing the predictive performances of the observed independent predictors for upgrading, we constructed

Table 3
Univariate analysis for prediction of GS upgrading

	Univariate analysis	
	OR (95% CI)	P value
Age	1.002 (0.978, 1.027)	0.8583
BMI	0.996 (0.946, 1.049)	0.8833
Preop PSA (categorical)		
(5.6–8.9) vs. <5.6	1.33 (0.87, 2.02)	0.944
>8.9 vs. <5.6	1.72 (1.14, 2.59)	0.024
Preop PSA (log scale)	1.691 (1.339, 2.137)	<0.0001
Prostate volume (log scale)	0.537 (0.363, 0.794)	0.0018
PSA density (log scale)	1.943 (1.524, 2.477)	<0.0001

ROC curves that showed adequate performance of only PSA density (log) (data not shown). The area under the curve (AUC) of PSA density (log) was 0.63 (95% CI: 0.59, 0.67). A LOESS plot was generated to describe GS upgrading as an interdependent function between prostate volume and Gleason biopsy sum category and to estimate the probability of upgrading for each Gleason biopsy sum subgroup. In this model, the risk

of upgrading in patients with Gleason biopsy sum ≥ 7 remained close to 15% regardless of prostate volume, while the probability of upgrading for patients who had Gleason biopsy sum < 7 became progressively higher as prostate volume decreased (Fig. 1A). When looking at prostate volume stratified by PSA range, small prostate volume was associated with higher probability of upgrading only in patients with PSA < 8.9 ng/ml (Fig. 1B).

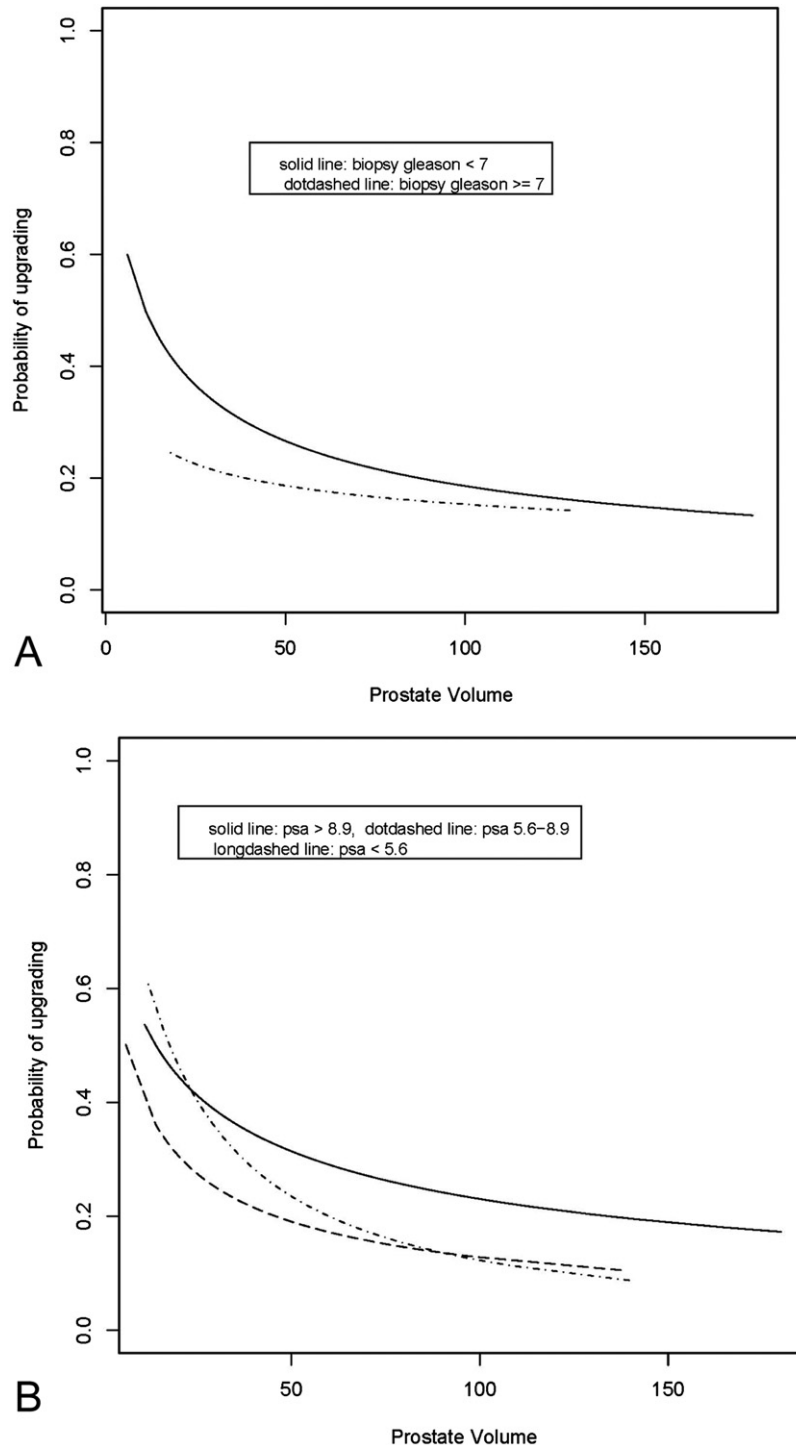


Fig. 1. LOESS plots of the risk of upgrading as a function of prostate volume stratified by GS category (A) or stratified by preoperative PSA range (B).

Age and BMI failed to predict GS upgrading ($P = 0.8583$ and $P = 0.8833$, respectively) (Table 3).

GS upgrading was associated with an adverse pathologic outcome at RP compared with the group of no upgrading (Table 2), which included higher rates of ECE (44% and 15%, respectively; $P < 0.001$), seminal vesicle invasion (18% and 5%, respectively; $P < 0.001$), positive surgical margins (30% and 13%, respectively; $P < 0.001$), and lymph node metastasis (10% and 1.5%, respectively; $P < 0.001$) (Table 2). The biochemical recurrence-free survival for upgraded patients was 86.8% vs. 94.9% for patients with no GS upgrading. However, this finding was not significant ($P = 0.07$). This secondary analysis included 227 patients with available PSA information; the mean (range) follow-up was only 10.2 (3–36) months.

4. Discussion

Patients with prostate cancer have a variety of treatment options ranging from active surveillance, radiotherapy, ablative therapy, to RP. Clinical decision making strongly depends on biopsy GS, which, however, often shows disparity with pathologic GS [9,12,17–19]. Active surveillance has been recommended for patients with low-risk prostate cancer [20]. One main requisite for choosing patients for this management is a Gleason sum ≤ 6 . When selecting patients for active surveillance, it is therefore critical to identify those patients who are at high risk for Gleason sum upgrading. The same is true for low-risk patients who are selected for brachytherapy. Moreover, the addition of hormonal therapy to radiation in patients with high-risk local prostate cancer has been shown to lead to survival benefit [21,22]. Finally, in patients with low-risk prostate cancer, the need for pelvic lymph node dissection is controversial [23], which once again shows that the assessment of accuracy with which the biopsy Gleason predicts the actual pathologic GS is of utmost importance for therapy choice.

Contemporary literature has been discordant with regard to potential predictors of GS upgrading, including preoperative PSA, prostate volume, and obesity. The majority of series consisted of either low-risk patients or intermediate and high-risk patients.

We report our experience with clinicopathologic variables in predicting GS upgrading at final pathology in an unfiltered, heterogeneous cohort of patients who underwent open RP at our institution. Pathologic GS was upgraded in 203 (29.7%) patients, while in 481 (70.3%) patients no GS upgrading was seen. We found preoperative PSA value, prostate volume, and PSA density to be significant predictors of upgrading at RP in both uni- and multivariate analyses.

A significant association of small prostate volume and preoperative PSA with GS upgrading has been first reported by D'Amico et al. and has been subsequently reinforced by several groups [12,13,24,25]. However, in a study by

Kulkarni et al., the association between small prostate volume and GS upgrading could not be shown [4]. In a previous study, the same group even reported an increase of the number of cancers upgraded at prostatectomy with increasing prostate volume quartile [11]. One reason for these contradictory findings most probably evolves from the differences in study populations. Underlining this, we show here that the strong relation of prostate volume and GS upgrading is diluted in patients with preoperative PSA level > 8.9 ng/ml. Turley et al. tried to reconcile the disparate reports arguing that the association of small prostate size and upgrading might depend on the number of cores taken, with an extended biopsy representing a more thorough sampling. In their study they found small prostate volume to be associated with GS upgrading only in patients who underwent extended biopsy [26]. On the other hand, previous studies have shown lower rates of GS upgrading with extended biopsy schemes [27]. The vast majority of the patients in the present study underwent extended biopsy in an outside institution. Thus, we were unable to control for the exact number of cores. While several groups have not been able to find any relation between number of biopsy and accuracy of Gleason grade, indicating that the extent of sampling is not a strong contributor in the context of GS upgrading [5,7], other groups have reported that a lower number of biopsy cores predicts GS upgrading [9].

As an alternative explanation for more GS upgrading in smaller prostates, biologic reasons have been discussed. A possible reason of more upgrading in patients with small prostates might be the fact that small prostates are more likely to harbor high-grade disease and to be associated with higher biochemical recurrence rates [8]. This is supported by our results showing a strong association of smaller prostate volume with higher probability of upgrading only in patients with GS ≤ 6 .

Preoperative PSA levels have been shown to be associated with GS upgrading in numerous studies [7,10]. PSA level significantly predicted GS upgrading in our series when included in the regression model as a continuous variable in the log scale. When used as a categorical variable, a PSA > 8.9 ng/ml predicted upgrading, but there was no significant difference in Gleason upgrading comparing PSA categories < 5.6 vs. 5.6–8.9 ng/ml. Conformingly, current literature shows inconsistencies regarding this potential predictor as well with several publications showing preoperative PSA as unrelated to GS upgrading [28,29]. This might be explicable arguing that a study population consisting of more patients with larger prostates will naturally have higher PSA levels. To bypass this fact, PSA density has been evaluated and described as significant predictor of Gleason upgrading and disease upstaging [29]. It has been proposed that the positive association of small prostate size and GS upgrading was attributed to higher resulting PSA density. Indeed, a higher PSA density value representing a relatively small prostate volume making

more PSA was the best predictor of the risk of Gleason upgrade in our cohort and resulted in improved receiver operating characteristics compared with preoperative PSA value or prostate volume alone.

We did not find a relation of age or BMI to GS upgrading. Intuitively it makes sense since elderly patients as well as patients with higher BMI have been shown to present with higher grade tumors [30], which, for apparent reasons and as we and others could show, are upgraded less frequently than tumors with Gleason biopsy sum ≤ 6 . However, the European cohort presented here consisted of thinner men with a mean BMI of 26.6 kg/m² compared with American cohorts.

There are several important limitations to our study. First and foremost are the limitations inherent to retrospective analyses. Furthermore, our study is limited by selection bias for patients undergoing surgery and by lack of central pathologic review. PSA density in our study derived from pathologic weight and not from TRUS volume depending on the assumption of a close correlation between pathologic weight and TRUS volume, which, however, has been well documented [14,15]. Finally, biochemical recurrence-free survival data were only partly available and very short-term, not allowing terminal conclusions; however, this was not a focus of our study.

In conclusion, in this study of men undergoing RP for prostate cancer, preoperative PSA, prostate volume, and PSA density were significantly associated with Gleason sum upgrading. Prostate volume was linked to GS upgrading, especially in low-risk patients. These parameters may be useful predictors for identifying patients who are at risk of GS upgrading, which was associated with adverse pathologic outcome. While our data suggest the strongest role for PSA density in prediction of GS upgrading and reinforce its utilization, the findings presented in this study also underline the necessity of large, multi-institutional approaches with subgroup analyses to clarify the true ability of reported variables to predict the aggressive potential of prostate cancer detected in biopsy. This has important implications, not only in patients who are candidates for watchful waiting and active surveillance strategies, but also in patients receiving nonsurgical therapy with lack of the benefit of complete information from the RP specimen.

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