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## What Are the Predictive Factors for Gleason Score Upgrade following RP?

### Key Words

Gleason score · Prostate cancer · Radical prostatectomy · Pathological outcomes · Upgrade

### Abstract

The Gleason score is one of a number of factors used in staging patients diagnosed with prostate cancer and in determining the treatment path such patients will ultimately follow. However, discrepancies in the Gleason scores obtained through biopsy compared with the final pathological staging of specimens following radical prostatectomy are not uncommon. Incorrect Gleason scoring can potentially influence treatment decisions and therefore, it is imperative that research is undertaken to elucidate factors that may be able to predict whether a patient's Gleason score might need to be reconsidered. A literature review was undertaken in late 2014 to highlight some of these factors that require further investigation.

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ingly radical prostatectomy (RP) is being used to treat the disease while it is still localised [2]. The pathological parameters of prostate cancer are well described utilizing the Stanford technique [3]. The essential reporting elements for specimens obtained via RP are Gleason score (primary plus secondary and tertiary patterns), location of tumour/dominant tumour mass, extraprostatic extension (presence, extent, location), seminal vesicle invasion, positive surgical margins (presence, location), treatment-related changes, and the T-stage [4]. More generally, Gleason score is prognostic of the aggressiveness and likelihood of progression of prostate cancer; however, it has been observed that there is a low correlation between the Gleason score at TRUS biopsy and the Gleason score observed after RP [5]. Undergrading and overgrading of biopsy specimens can lead to potential under-treatment and overtreatment, respectively, of men with prostate cancer [6], and therefore, it is important that research into factors predictive of Gleason score discordance be undertaken.

### Introduction

The incidence of prostate cancer in Australia is 104.2 per 100,000, the highest in the world [1], likely due to more widespread PSA surveillance allowing for increased detection. The upsurge in PSA surveillance in recent years has driven a shift towards earlier diagnosis, and increas-

### Methods

A Medline search was performed in late 2014, using the search terms 'oncological', 'outcomes', 'prostate cancer', 'radical prostatectomy', 'Gleason score' and 'pathological upgrade'. Advanced search parameters included English language abstracts and publication dates limited from 2000 to present. Other articles for contextual background were obtained through more general searches of the literature.

## Discussion

### *Gleason Score Discordance following RP*

In 2005, the International Society of Urologic Pathology revised the Gleason scoring system such that it is now derived from totalling the most common and the highest Gleason patterns in a biopsy specimen [6]. However, Gleason score upgrade and downgrade, defined by Epstein et al. [6] as the increase or decrease, respectively, of Gleason scores in prognostic grade (5–6, 3 + 4 = 7, 4 + 3 = 7, 8 and 9–10), is a phenomenon well described among men diagnosed with clinically low risk disease who undergo RP as primary treatment [5]. Tumour upgrade of any score is associated with amplified aggressiveness, which increases the potential for recurrence and adverse prognosis [7]. Therefore, it is an important consideration in the management of prostate cancer because inaccurate biopsy Gleason scores pose a risk of inappropriate treatment [8]. The TRUS biopsy and RP specimen Gleason scores may be discordant for several reasons, namely pathologist grading error, borderline grades, or sampling errors [6]. Rates of Gleason score discordance are high, with a study by Seisen et al. [9], reporting overall upgrading of Gleason scores of 56.7%, while Vellekoop et al. [10] report levels of approximately 50%.

Contemporary studies into Gleason score discordance have focused on variables that could be used as predictive factors. Epstein et al. [6] utilized multivariable logistic regression analysis to determine factors predictive of upgrade from a biopsy Gleason score 5–6 on RP. These factors included increased age, increased preoperative serum PSA levels, increased maximum percentage of cancer per core biopsy and a decreased specimen weight following RP. Conversely, predictors of downgrading from a biopsy 3 + 4 = 7 were lower levels of serum PSA, lower maximum percentage of cancer per core and a higher specimen weight. Decreased specimen size is hypothesised to predict adverse pathology due to a smaller prostate being representative of decreased intra-prostatic androgen levels such that only more dedifferentiated epithelial cells survive [11]. Sfoungaristos et al. [5] found that a prostate specimen volume <34.5 ml following RP was significantly associated with upgrade in patients with preoperative Gleason scores ≤6, as well as a PSA density >0.155 ng/ml. PSA density is a parameter calculated by dividing the preoperative PSA value by the TRUS-estimated prostate volume [7], representing a strong predictor of Gleason upgrade.

Truong et al. [11] assessed more than 30 clinicopathological parameters in biopsy Gleason ≤6 patients who underwent RP and were found to have Gleason score up-

grade (defined as Gleason score ≥7) to develop the BADGR nomogram for risk stratification of low-risk patients. Pathological parameters at initial biopsy, clinical factors and pathological parameters at final pathology were analysed. Pathological factors associated with upgrading were a smaller prostate specimen, increased per cent positive pathological slides, per cent tumour volume, pathological stage, extraprostatic extension, PSM and bilateral disease. PSA density, obesity and prostate size were clinical predictors of Gleason upgrading. Family history, smoking status and clinical stage were not found to predict upgrade, while Jalloh et al. [12] has further noted that although African American men carry a higher burden of prostate cancer, they did not note any statistically significant difference in rates of upgrading between racial groups, indicating that race is not a predictive factor.

Vellekoop et al. [10] noted that while candidates for active surveillance are selected on the basis of biopsy Gleason score, clinical stage and PSA levels, additional predictors could improve treatment allocation. This study considered 4,500 men who with Gleason 6, T1c/T2 stage disease underwent RP and examined variables associated with adverse pathology, which was defined as upgrading to Gleason ≥7, or upstaging to ≥pT3 disease. Factors associated with adverse pathology were age >60, higher PSA levels, a PSA density >0.15 ng/ml/cm<sup>3</sup>, palpable disease, and cancer extending >4 mm on biopsy. Again, larger prostate specimens were inversely related to adverse pathology. The investigators advocate that PSA density and extent of cancer on biopsy cores should be utilised as inclusion criteria for active surveillance along with the pre-existing criteria. Seisen et al. [9] developed a prognostic score for patients diagnosed with Gleason ≤6 disease as a screening tool for upgrading. They found that the best independent predictive factor for upgrading was a core biopsy cancer length of >5 mm (given a score of 5), followed by a preoperative PSA level >15 ng/ml and age >70 (given scores of 4 and 3, respectively). Conversely, TRUS evaluation of prostate weight >50 g as well as >12 core biopsies (both scores of –2) were protective against upgrading. The investigators reported a probability of upgrading of 71.2% for a Gleason ≤6 patient with a score of >2.

Recently, Mearini et al. [13] investigated the potential role of the PSA isoform p2PSA as well as some of its derivatives: the percentage of p2PSA to free PSA (%p2PSA) and the Prostate Health Index (PHI). The primary endpoint of this study was to elucidate the value of these biomarkers p2PSA, %p2PSA and the PHI as potential preoperative indicators for characteristics of heightened tumour aggressiveness, including the presence of a Gleason

score  $>/8$  and the occurrence of Gleason score upgrade at RP. On univariate analysis, p2PSA significantly predicted Gleason score upgrading (OR 1.019,  $p = 0.027$ ), while on bivariate analysis, the p2PSA, %p2PSA and PHI were accurate prognosticators of a final Gleason score  $>/8$ . At multivariate analysis, the PHI was an independent predictor of high-risk disease (which the authors defined as pT3 and/or Gleason score  $>/8$  and/or N1). The authors conclude that these biomarkers are indeed strong predictors of overall tumour aggressiveness, providing for more accurate prognostications than the currently utilized clinical markers. However, they note that further studies are necessary to validate their conclusions. Indeed, the potential value of p2PSA as a biomarker for Gleason score upgrade is something that needs to be more thoroughly investigated as a result of these findings.

Therefore, it appears that the clinical risk factors for an upgrade in Gleason score after RP include PSA density  $>0.15$  ng/ml, extension of cancer for  $>4$  mm on core biopsies, prostate volume  $<34.5$  ml, obesity, advanced age ( $>60$ ) and higher preoperative PSA levels (table 1). A larger sized prostate and a greater number of core biopsies appear to be the main protective factors against upgrading the Gleason score. The p2PSA, %p2PSA and PHI require further trialling before they can more definitively be said to predict the occurrence of Gleason score upgrade at RP.

However, another potent influence on the accurate reporting of Gleason scores exists in the guise of inter-pathology variance. Discordant evaluation by individual pathologists introduces a measure of human error into the diagnostic process. Netto et al. [14] investigated the level of agreement between local pathologist reports and central pathologist findings using data from the TAX 3501 trial. Specialized urologists reassessed the local pathologist reports of 257 consecutive cases and it was found that they confirmed the Gleason score only in 70% of cases. This highlights that significant interobserver variations do occur among pathologists. Kuroiwa et al. [15] presented similar findings. In this study, dedicated central pathologic review utilizing the International Society of Urologic Pathology consensus statement significantly increased the concordance rates between biopsy Gleason score and the final Gleason score at RP, reducing the rates of Gleason score upgrade, when compared with the local pathologist review ( $p \leq 0.05$ ). In a separate study by Goodman et al. [16], it was noted that the level of agreement between local pathology reports and central review depends on the type of diagnosing facility (with a higher level of discordance found in small community hospitals), but also on the level of expertise and specialization of the individual

**Table 1.** Predictive factors for Gleason score upgrade identified in the literature

Clinical variable	Comment
PSA density	Levels $>0.15$ ng/ml appear to be a risk factor for pathological upgrade (5, 7, 10, 11)
Histological extent of tumour	Extension through cores $>4$ mm appears to be a risk factor (6, 9, 10, 11)
Prostate volume	TRUS estimated prostate volumes $<34.5$ ml appear to be a risk factor for pathological upgrade, while volumes $>50$ ml appear to be predictive of pathological downgrade (5, 6, 7, 9, 10, 11)
Obesity	Appears to be a risk factor for upgrade (11)
Age $>60$	Appears to be a risk factor for pathological upgrade (6, 9, 10)
Higher preoperative PSA value	Appears to be a risk factor for pathological upgrade (6, 9, 10)
$>12$ biopsy cores	It appears that the higher the number of cores, the more accurate the Gleason scores (9)
Clinical stage	Appears to be no association (11)
Racial background	Appears to be no association (12)
Smoking status	Appears to be no association (11)
Family history	Appears to be no association (11)
p2PSA, %p2PSA and PHI	Appears to have some promise as a clinical marker; however, further investigation is required (13)

pathologist. Of course, the economic feasibility of widespread urologist review presents a challenge; however, from these studies it has to be inferred that evaluation by dedicated urologists presents an obvious means of reducing rates of Gleason score upgrade.

### Future Directions

PSA density warrants further investigation as a predictive tool for Gleason upgrading. In the study by Truong et al. [11], every 0.1 unit increase in PSA density yielded an odds ratio of 1.72 for upgrading the Gleason score. Sfoungaristos et al. [7] found that PSA density was more accurate than PSA alone for predicting upgrading at a threshold value of 0.15 ng/ml. At this cut-off, sensitivity for predicting upgrading was 75.4%, specificity 42.1%, positive predictive value 55.8% and negative predictive

value 69.6%. However, results from a study by Mearini et al. [13] indicate that a lower cut-off value of 0.085 ng/ml further reduces rates of advanced disease. Further insight is also required into the relationship between PSA density and prostate specimen volume. Australian data regarding PSA density and Gleason upgrading is required to assist in drawing more accurate consensus as to the value of PSA density as a clinical tool. The merit of p2PSA, %p2PSA and PHI in predicting Gleason score upgrade is another area that requires the support of Australian data.

## Conclusions

Incorrect biopsy Gleason scores can adversely impact the optimal treatment of men with prostate cancer, and under-treatment of potentially high-risk cancers is a real possibility. The factors behind why upstaging occurs at such high prevalence in populations around the world remain to be conclusively determined; however, the role played by the variables we have listed earlier warrant further examination.

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