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Multiple cores of Gleason score 6 correlate with favourable findings at radical prostatectomy

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Abstract

- To establish whether the good prognosis of Gleason score 6 (GS6) is maintained in the setting of multiple involved cores.
- In total, 6156 men (from 1 April 2000 to 30 April 2007) with GS6 on biopsy underwent radical prostatectomy (RP) at our institution.
- The number of positive cores was correlated with the outcome at RP.
- More positive cores correlated with less organ-confined disease ($P < 0.001$), positive margins ($P < 0.012$), increasing RP grade ($P < 0.001$) and increased seminal vesicles/lymph node involvement ($P = 0.012$).
- For men with data available, the actuarial risk of being biochemically free of disease at 5 years was 93.2% when 6 cores were positive (812 men followed to 5 years) vs 89.1% if >6 cores were positive (41 men followed to 2 years) ($P = 0.6$).
- Although the predicted 'cure rate' of >75% probability of a tumour showing no evidence of biochemical recurrence at 10 years after RP was statistically different between cases with 6 vs >6 positive cores ($P < 0.0001$), the outcome in both groups was still favourable (90.5% vs 84%).
- Partin-like tables were generated factoring in the number of positive cores to predict organ-confined disease as a guide for urologists to perform nerve-sparing surgery.
- For example, with T1c disease, there was a 75% probability of organ-confined disease with one to three positive cores regardless of prostate-specific antigen (PSA) level, and the same probability was present with four to six positive cores and a PSA level of 0–4 ng/mL.
- A low Gleason score on biopsy is a powerful prognostic finding, such that this favourable outcome is maintained even in the setting of multiple positive cores with GS6.

Keywords

Gleason score 6; needle biopsy; radical prostatectomy

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Conflict of Interest

None declared.

Introduction

Gleason score (GS) is one of the most powerful predictors of prognosis in adenocarcinoma of the prostate. It is commonly factored into various probability tables and nomograms to predict outcome and to estimate the pathological stage at radical prostatectomy (RP). For example, Partin tables incorporate the preoperative PSA level, Gleason score and clinical TNM stage into nomograms to predict the stage at RP [1]. Han tables correlate preoperative PSA level, postoperative Gleason score and pathological stage to predict the probability of biochemical recurrence up to 10 years after surgery [1]. Kattan's pretreatment nomogram predicts pathological stage, which factors in PSA, age, Gleason score (as continuous variables), clinical stage and fraction of positive biopsy cores [2,3]. The D'Amico preoperative risk classification system was also shown to fairly accurately stratify men in terms of their risk of biochemical recurrence, metastases and death [4,5]. Although there is a general correlation with increasing cores and adverse findings at RP, the prognostic significance of multiple cores with Gleason score 6 (GS6) has not been specifically addressed.

Patients and Methods

The present study included 6156 consecutive men with GS6 with TRUS-guided prostate core biopsy who underwent RP at our institution between 2000 and 2007. RP specimens were sectioned serially and submitted in their entirety. The number of positive cores was analyzed in relation to the outcome at RP (percentage organ-confined, margin status and Gleason score). To assess the relationship between the number of positive cores and progression, two analyses were performed. Follow-up information was available in 3156 men, where we were able to calculate the actuarial risk of biochemical progression. To estimate the risk of progression for the whole cohort, we established a 'cure rate', which was defined as a >75% probability of a tumour showing no evidence of biochemical recurrence at 10 years after RP, utilizing the Han table based on presurgical PSA level, pathological stage and post-surgical Gleason score. We also evaluated the fraction of positive cores (positive cores/total cores); however, the number of positive cores and fraction of positive cores was so tightly correlated ($r = 0.94$) that there was no meaningful difference between the two variables and only the number of positive cores was utilized.

All tissue samples were interpreted by a small group of general surgical pathologists with extensive experience in urological pathology, with a review of selected cases by the senior author (J.I.E.) at a daily case review conference. Significance testing was performed for continuous variables using a *t*-test for the comparison of means. For dichotomous variables, the Pearson's chi-square test was performed. $P < 0.05$ was considered statistically significant. Logistic and Cox regression analyses were used to compare multiple variables with single endpoint and censored data, respectively. All statistical analyses were performed using STATA, version 12 (StataCorp LP, College Station, TX, USA).

Results

A summary of the clinicopathological data is provided in Table 1. The mean number of positive cores was 2.5 ($n = 1-16$). The differences between cases with ≤ 6 positive cores compared to >6 positive cores was significant for percentage organ-confined disease ($P < 0.001$), margins ($P = 0.012$) and the pathological percentage of cases with RP GS6 ($P < 0.001$) (Table 2). Positive seminal vesicles or lymph nodes were seen in 1.5% (90/5863) and 3.5% (10/289) of cases with 1-6 vs >6 positive cores, respectively ($P = 0.012$). Table 3 was generated based on clinical stage (T1c vs T2), number of positive cores and preoperative PSA level to predict organ-confined disease. For example, with non-palpable disease (T1c),

there was a 75% probability of organ-confined disease with one to three positive cores regardless of PSA, or with four to six positive cores and a PSA level of 0–4 ng/mL.

For the men with data available, the actuarial risk of being biochemically free of disease at 5 years was 93.2% when 6 cores were positive (812 men followed to 5 years) vs 89.1% if >6 cores were positive (41 men followed to 2 years) ($P = 0.6$). Although the predicted 'cure rate' of >75% probability of a tumour showing no evidence of biochemical recurrence at 10 years after RP was statistically different between cases with 6 vs >6 positive cores ($P < 0.001$), the outcome in both groups was still favourable (90.5% vs 84%) overall (Table 2).

Discussion

Based on clinicopathological parameters, various probability tables and nomograms have been created to predict outcome and estimate the pathological stage at RP in prostatic adenocarcinoma. Nomograms offer the advantage of allowing users to quantify the combined contribution of several risk factors, and provide a predicted probability of the event of interest.

At the Brady Urological Institute at the Johns Hopkins Hospital, the original Partin tables were developed by Alan W. Partin and colleagues in 1993. Revised in 2001, 2007 and 2011, the Partin tables factored clinical stage, preoperative PSA level and biopsy Gleason score to predict the pathological stage at RP. A 2007 revision to the Partin tables aimed to use these variables with a contemporary patient cohort to correct for the effects of stage migration with the trend of newly-diagnosed patients who present with local or regional disease. In 2011, an additional update allowed continuous PSA values, resulting in a 2010 Partin nomogram [6].

The Partin tables, along with other predictive tables and nomograms, including the Han tables [1], Kattan nomograms [2,3] and Cancer of the Prostate Risk Assessment (CAPRA) scores [7,8], all have the Gleason score as one of their strongest predictive variables. With an increasing Gleason score, there is a strong correlation with increased pathological stage and the risk of progression after RP. Conversely, GS6 disease on biopsy is associated with favourable outcomes.

Many studies have also shown that an increasing number of biopsy cores with adenocarcinoma correlates with a worse outcome at RP [9,10]. Some of the aforementioned tables account for tumour extent on biopsy. For example, Kattan's pretreatment nomogram predicts pathological stage, which factors in PSA level, age, Gleason score (as continuous variables), clinical stage and fraction of positive biopsy cores [2,3]. The CAPRA score assesses the risk of extraprostatic extension, factoring in Gleason score, stage, biopsy cancer extent, age and serum PSA levels [7,8]. Although it appears that, by using the above tables and nomograms, the same question could be assessed in the present study, the data are not comparable. Predictive nomograms and tables are based on logistic regression or Cox regression analyses and the numbers generated for each combination of variables may be based on either no or only a few patients with this combination of clinical-pathological findings. For example, a nomogram could be used to predict the risk of non-organ-confined disease in the setting of eight biopsy cores positive with GS6. However, there would be no way of specifically knowing whether any patients (or how many patients) had these findings. Even with large data sets, there may be only a few patients with discordant findings (ie. extensive yet lower grade cancer). The urologist can now have greater confidence in the predicted outcome for their patient with these discordant findings using data from the present study; the presented table lists the actual number of cases with GS6, stratified by the number of positive cores along with outcome. This information can be used,

for example, in the decision of whether to spare the neurovascular bundles in the setting of extensive GS6 adenocarcinoma.

Many studies concentrate on the risk of ‘upgrading’, which corresponds with a higher Gleason score at RP than originally seen on biopsy. However, a more useful prognostic outcome is the risk of organ-confined disease, positive margins and the probability of postoperative cure, as analyzed in the present study. We show that favourable outcomes are still maintained despite an increasing number of positive cores as long as a GS6 is maintained. The data of the present study show that Gleason score to some extent outdoes tumour extent on biopsy as a predictive parameter. Data from the CAPRA score similarly show the relative greater prognostic impact of Gleason score, in that the Gleason score had a disproportionate weight where the maximum 3 points assigned to the highest Gleason score is more than that which can be achieved with maximum biopsy cancer extent [7,8].

More than 89% of patients with >6 positive cores of GS6 were biochemically free of disease at 5 years. The findings associated with poor outcomes at RP (non-focal extra-prostatic extension and positive lymph nodes or seminal vesicles) were seen in only a small percentage of patients with multiple (up to 10) positive cores of GS6. A low Gleason score on biopsy is a powerful prognostic finding, such that this favourable outcome is maintained even in the setting of multiple positive cores with GS6.

Although the present study shows that even multiple cores of GS6 are associated with relatively favourable findings at RP, a limitation of the present study is the question of whether the study cohort benefited from treatment with RP or whether they were overtreated. There is a correlation between an increasing number of positive cores with GS6 on biopsy and upgrading to Gleason score 7 on radical prostatectomy, and most current protocols for active surveillance are restricted to men with relatively few positive cores of GS6 adenocarcinoma. Whether more cores of GS6 on biopsy are acceptable for active surveillance requires long-term follow-up studies.

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Abbreviations

CAPRA	Cancer of the Prostate Risk Assessment
GS6	Gleason score 6
RP	radical prostatectomy

What's known on the subject? and What does the study add?

- Previous studies have reported variable outcomes at radical prostatectomy (RP) with Gleason score 6 (GS6) on biopsy. It has been shown that a significant proportion of patients with GS6 disease at biopsy are upgraded to Gleason score 7 or higher after RP, increasing the risk of an adverse outcome. However, such studies have focused on clinical parameters such as PSA, prostate volume and biopsy cancer volume, in concert with GS6, to predict clinically significant upgrading.
- The present study is the first to use a significant number of patients with the aim of specifically analyzing the outcome at RP (i.e. percentage organ-confined, margin status, overall grade and biochemical recurrence) and making a direct correlation with the number of positive cores to show that the overall prognosis is favourable.

Table 1

Summary of the clinicopathologic data of the patient cohort in the present study.

Clinical variable	Value
Age (years), mean (SD)	57.3 (6.4)
Preoperative PSA level (ng/mL), mean (SD)	5.8 (3.8)
Positive cores, <i>n</i> (median, range)	2.5 (2, 1–16)
Involvement of cores (%), mean (SD)	39.3 (28)
Race (%)	
Caucasian	87.4
African-American	8.0
Asian	1.0
Clinical stage (%)	
T1c	81.0
T2a	14.2
T2b	2.8
Tx	1.5
Pathological stage (%)	
Organ-confined	81.9
Focal EPE	8.3
Non-focal EPE	8.2
SV/LN	1.6

EPE, extraprostatic extension; LN, lymph node involvement; SV, seminal vesicle invasion.

Table 2

Correlation between estimated cure rate, percentage organ-confined, margin status and grade at radical prostatectomy vs the number of positive cores.

Number of positive cores	Cure rate 75% (%)	Organ-confined (%)	Negative margins, % (n/N)	Radical prostatectomy GS6, % (n/N)
1-6	90.5	82.5 (4828/5851)	89.3 (5226/5850)	77.2 (4509/5843)
>6	84.0	68.3 (198/290)	85.2 (247/290)	66.4 (192/289)
1	93	88 (2219/2525)	93 (2342/2525)	82 (2051/2514)
2	90	83 (1214/1462)	88 (1294/1464)	75 (1105/1465)
3	89	77 (629/812)	88 (715/811)	74 (603/814)
4	88	77 (385/501)	86 (430/501)	70 (349/499)
5	86	70 (229/326)	80 (260/326)	72 (237/327)
6	84	67 (151/224)	82 (183/223)	73 (164/224)
7	85	64 (80/125)	83 (105/126)	70 (88/125)
8	85	77 (58/75)	87 (65/75)	64 (48/75)
9	81	62 (23/37)	89 (33/37)	68 (25/37)
10	83	71 (37/53)	85 (44/52)	63 (54/85)

Table 3

Percentage organ-confined disease by preoperative PSA level and the number of positive cores, stratified into the two most commonly occurring clinical stages of disease (T1c and T2).

Number of positive cores	PSA level 0–4 ng/mL	PSA level = 4.1–10 ng/mL	PSA level > 10 ng/mL
T1c, <i>n/N</i> (%)			
1–3	1011/1105 (91.5)	2126/2514 (84.6)	274/362 (75.7)
4–6	161/189 (85.2)	391/527 (74.2)	30/57 (52.6)
>6	29/35 (82.9)	71/109 (65.1)	10/17 (58.8)
T2, <i>n/N</i> (%)			
1–3	317/349 (90.8)	223/313 (71.2)	25/50 (50)
4–6	74/100 (74)	81/136 (59.6)	9/17 (52.9)
>6	12/22 (54.6)	30/41 (73.2)	6/9 (66.7)