Predicting the Gleason sum of a patient with a prostate biopsy core Gleason ≤7 and a prostate biopsy core Gleason ≥8

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Abstract

Introduction: We review a subset of men who had discordant prostate biopsy sums and were treated with radical prostatectomy.
Methods: Consecutive patients treated with radical prostatectomy at The Ottawa Hospital between 2000 and 2012 were reviewed. Those with at least 1 prostate biopsy core of Gleason sum ≥8 *and* at least 1 prostate biopsy core of Gleason sum ≤7 cancer were included.
Results: Of the 764 radical prostatectomies, 661 (87%) were eligible for the study and 35 (5%) met inclusion criteria. Of these, only 16 (46%) had prostatectomy Gleason sum of ≥8. When the highest biopsy core was Gleason sum 8 (n = 24), only 7 (29%) had a prostatectomy Gleason sum ≥8. When the highest biopsy core was Gleason 9 (n = 11), 9 (82%) had a prostatectomy Gleason sum ≥8 (relative risk [RR] 2.8; $p = 0.004$). Patients with clinical T3 tumours were at higher risk of Gleason sum ≥8 compared to cT1 patients (RR 3.7; $p = 0.008$). Patient age ($p = 0.89$), preoperative prostate-specific antigen ($p = 0.34$), prostate volume ($p = 0.86$), number of biopsy cores ($p = 0.18$), and proportion of biopsy cores with cancer ($p = 0.96$) were not strongly associated with risk of prostatectomy Gleason sum ≥8.
Conclusion: These data should be considered when assigning patients into prognostic risk categories based on prostate biopsy information. Further study to verify our findings using larger samples is warranted.

Introduction

The Gleason tumour grading system has provided important prognostic information for men with prostate cancer for over 40 years.[1,2] Contemporary Gleason grades range from 3 to 5 and these are most predictive of a patient's prognosis when 2 of the tumour grades are added together (Gleason sum range between 6 and 10). The prostatectomy Gleason sum is determined by adding the most common tumour grade and the second most common tumour grade from the prostatectomy specimen. However, some men diagnosed with prostate cancer will not elect to have a prostatectomy. The prostate biopsy information is therefore the only cancer tissue available in these patients to guide treatment decisions and estimate prognosis.

A standard prostate biopsy template includes at least 10 biopsy cores and pathologists use updated criteria for tumour grade assignment.[3-5] In contradistinction to the prostatectomy Gleason sum, the biopsy Gleason sum is defined as the *most common* Gleason grade added to the *highest* Gleason grade observed. It is common for each needle biopsy core with cancer to be assigned an independent Gleason sum.[3,6] Therefore, a patient may have several prostate biopsy cores that contain cancer, and each core could be assigned a different Gleason sum.

A challenging scenario for clinicians is when a patient has 1 or more biopsy cores with a high Gleason sum (≥8), and at least 1 other core reveals a low or intermediate Gleason sum (≤7). While it is generally believed that the core with the highest sum should be used when assigning cancer risk, controversy exists, and some may assign risk based on all of the biopsy tissue combined.[3,7-9] Indeed, the assigned biopsy Gleason sum may vary depending on the interpreting clinician.

Accurate assignment of biopsy Gleason sum is important, especially when a patient chooses radiotherapy instead of surgery, as the recommended duration of adjuvant androgen deprivation is different for a patient considered high-risk (Gleason ≥8) compared to a patient considered intermediate-risk (Gleason ≤7).[10] The purpose of this study was to review a cohort of men who had discordant prostate biopsy sums and were treated with radical prostatectomy. Our hypothesis was that most patients with at least 1 prostate biopsy core

of Gleason sum ≥8 *and* at least 1 prostate biopsy core of Gleason sum ≤7 will have a prostatectomy Gleason sum ≥8.

Methods

Consecutive patients treated with radical prostatectomy by 1 of 3 surgeons at The Ottawa Hospital between January 2000 and March 2012 were reviewed. Those with at least 1 prostate biopsy core of Gleason sum ≥8 *and* at least 1 prostate biopsy core of Gleason sum ≤7 were eligible. We excluded patients with incomplete pathological information, treated with preoperative androgen deprivation, and who were previously treated with prostate radiation. Institutional ethics review board approval was obtained prior to study commencement.

Clinicopathologic information was obtained from the medical record. Paraffin-embedded biopsy tissue samples were reviewed by an expert genitourinary pathologist. If the biopsy was performed at an outside institution, the tissue was obtained and re-reviewed by an expert genitourinary pathologist at our institution. Prostate biopsy information included: the number of cores obtained, the number of cores positive for cancer, the biopsy sum of each core, and the proportion of Gleason grade 3 cancer in each core. Intact prostatectomy specimens were fixed in formalin, inked to determine surgical margins in the fresh state, serially sectioned, and entirely submitted for histologic examination. Gleason grade and Gleason sum for biopsy cores and prostatectomy specimens were assigned using contemporary methods.[1] For biopsy cores, the most common Gleason grade was added to the highest Gleason grade. For the prostate specimen, the most common grade was added to the second most common grade. Furthermore, if there was a tertiary Gleason grade in the prostatectomy tissue, the proportion of tertiary grade tissue was documented.

We hypothesized that most patients with at least 1 prostate biopsy core of Gleason sum ≤7 *and* at least 1 prostate biopsy core of Gleason sum ≥8 will have a prostatectomy Gleason sum ≥8. We also hypothesized that the proportion of Gleason grade 3 cancer on biopsy was associated with prostatectomy Gleason sum. For example, patients with a large volume of Gleason grade 3 cancer on biopsy would be more likely to have a prostatectomy Gleason sum ≤7 (since Gleason grade 3 must be a component of a prostatectomy Gleason sum ≤7). To test this hypothesis, the amount of Gleason grade 3 cancer in the biopsy specimens was quantified and analyzed using 4 methods: (1) the *proportion* of Gleason grade 3 cancer from all biopsy tissue (Gleason grade 3 tissue/ all biopsy tissue), (2) the *proportion* of biopsy cores that contained any Gleason grade 3 cancer (number of cores with Gleason 3/total number of cores), (3) the *number* of cores that contained any Gleason grade 3 cancer, and (4) the *highest proportion* of Gleason grade 3 cancer in any one core (Gleason 3 tissue/biopsy core).

Summary statistics were generated and tabulated. The primary outcome was prostatectomy Gleason sum ≥8 (analyzed as a dichotomous variable Gleason ≥8 vs. Gleason ≤7). Unadjusted associations between candidate predictor variables and prostatectomy Gleason sum were determined using log-binomial regression. Relative risks (RR) >1.0 indicated that the candidate predictor was associated with increased risk of prostatectomy Gleason sum ≥8.

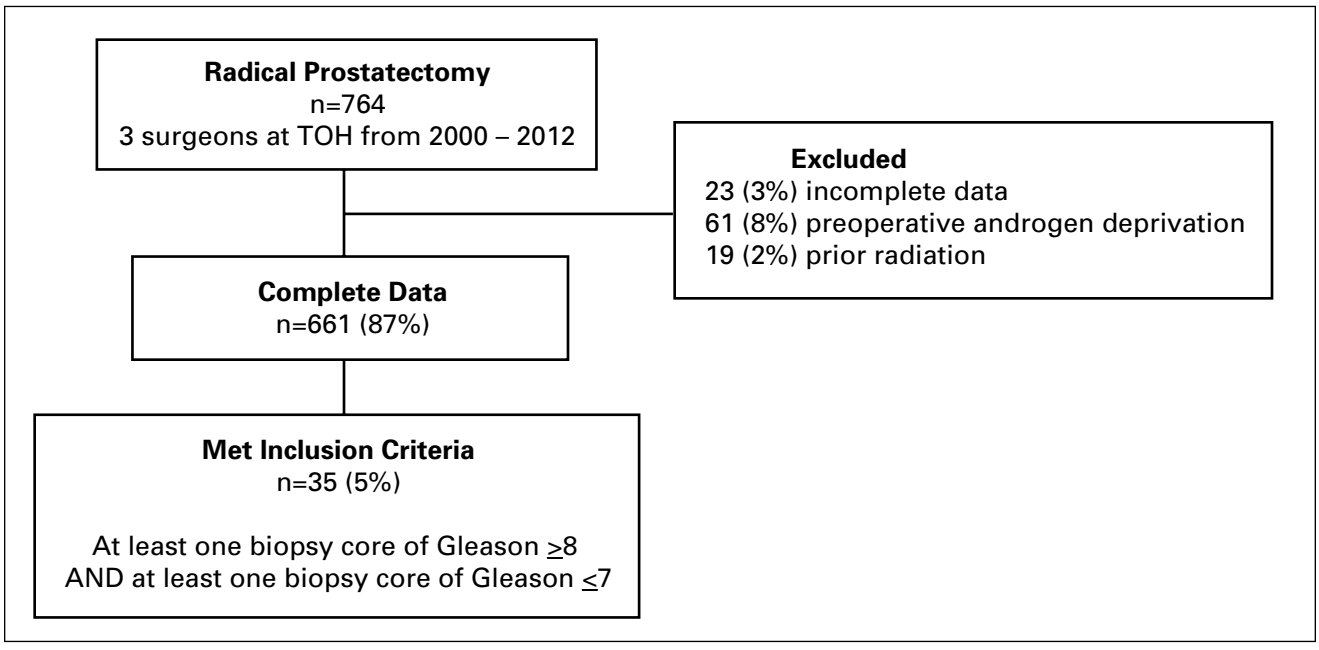

Fig. 1. Patient selection strategy using inclusion and exclusion criteria. TOH: The Ottawa Hospital.

Results

A total of 764 radical prostatectomies were performed by 3 surgeons at The Ottawa Hospital between January 2000 and March 2012. Twenty-three (3%) were excluded because of incomplete biopsy or pathology information, 61 (8%) due to preoperative androgen deprivation, and 19 (2%) due to prior radiation. Of the remaining 661 (87%) radical prostatectomy patients, 35 (5%) met inclusion criteria by having at least 1 biopsy core of Gleason sum ≥8 *and* at least 1 biopsy core of Gleason sum ≤7 (Fig. 1). The mean patient age was 62.8 years (standard deviation [SD] 6.7) and the mean preoperative prostate-specific antigen (PSA) was 8.8 (SD 7.7). Most (68%) patients had a clinically palpable tumour (Table 1). The median number of biopsy cores was 10 (interquartile range [IQR] 10-10) and the median number of positive cores was 5 (IQR 3-7) (Table 2).

Of the 35 patients, 19 (54%) had a prostatectomy Gleason sum ≤7 and 16 (46%) had a prostatectomy Gleason sum ≥8 (Table 3). When the highest biopsy core was Gleason sum 8 (n = 24), only 7 (29%) had a prostatectomy Gleason sum ≥8. When the highest biopsy core was Gleason 9 (n = 11), 9 (82%) had a prostatectomy Gleason sum ≥8 (RR 2.8; confidence interval [CI] 1.4, 5.6; $p = 0.004$).

Preoperative and biopsy information were stratified by prostatectomy Gleason sum (Table 1, Table 2). Higher clinical stage was associated with prostatectomy Gleason sum ≥8 (cT3 vs. cT1 RR 3.7, 95% CI 1.4-9.6). Patient age ($p = 0.89$), pre-operative PSA ($p = 0.34$), prostate volume ($p = 0.86$), number of biopsy cores ($p = 0.18$), and proportion of biopsy cores with cancer ($p = 0.96$) were not strongly associated with risk of prostatectomy Gleason sum ≥8 (Table 1, Table 2).

Contrary to our hypothesis, the amount of Gleason grade 3 biopsy tissue did not predict prostatectomy Gleason sum, regardless of the method used to quantify Gleason grade 3 (Table 2). The proportion of all biopsy tissue that was Gleason grade 3 was 5.3% for prostatectomy Gleason sum ≤7 versus 4.6% for prostatectomy Gleason sum ≥8 ($p = 0.66$). The respective mean *proportion* of cores that had Gleason grade 3 was 34% versus 25% ($p = 0.134$), the median *number* of cores that had Gleason grade 3 was 3 versus 1.5 ($p = 0.387$), and, on average, the *highest proportion* of Gleason grade 3 in any core was 29% versus 26% ($p = 0.69$). Six (31%) of the 19 patients with a prostatectomy Gleason sum ≤7 had a tertiary grade 5 (range 1% to 10% of prostatectomy cancer tissue).

Discussion

The prostatectomy Gleason sum is the most powerful predictor of survival for patients with clinically localized prostate cancer.[2,11] However, clinicians rely on biopsy Gleason sum, at least initially, to plan treatment and counsel patients. Despite refinement in grading criteria, there are situations when the overall tumour biopsy Gleason sum may be difficult to assign. In this study, we evaluated a specific situation when at least 1 biopsy core was Gleason ≥8 and at least 1 other was Gleason ≤7.

Contrary to our hypothesis, we observed that when a patient had a biopsy core of ≥8 and a discordant biopsy core ≤7, only 46% had a prostatectomy Gleason score ≥8. Among patients whose highest core was Gleason 8, only 29% had a prostatectomy Gleason sum ≥8. This was surprising and contradicted general opinion based on previously published data using older grading systems.[3,7-9] The proportion of *downgrading* we observed was higher than what was reported in a large series from Johns Hopkins. In that series, including all patients regardless of biopsy discordance, 49% had a prostatectomy Gleason score ≥8 when the highest biopsy core was Gleason 8.[12]

While we observed a high proportion of downgrading in patients whose highest core was Gleason sum 8, this was

Table 1. Preoperative clinical factors and associations with prostatectomy Gleason ≥8

Patient characteristics							
Candidate predictors	**All patients**	**Prostatectomy Gleason sum**		**RR**	**95% LCI**	**95% UCI**	***p* value**
		≤7	**≥8**				
Mean age in years (SD)	62.8 (6.7)	62.9 (5.8)	62.7 (7.9)	0.996	0.935	1.061	0.892
Mean preoperative PSA (SD)	8.8 (7.7)	8.0 (5.2)	9.9 (10.1)	1.016	0.984	1.048	0.336
Mean prostate volume (SD)	42. 6 (21.6)	42.0 (21.6)	43.3 (22.4)	1.001	0.986	1.017	0.860
Clinical stage (%)							
T1c	11 (31%)	8 (42%)	3 (19%)				
T2a	11 (31%)	8 (42%)	3 (19%)	1.833	0.641	5.248	0.259*
T2b	6 (17%)	2 (11%)	4 (25%)				
T2c	5 (14%)	1 (5%)	4 (25%)				
T3a	1 (3%)	0 (0%)	1 (6%)	3.667	1.397	9.624	0.008†
T3b	1 (3%)	0 (0%)	1 (6%)				

RP: radical prostatectomy; SD: standard deviation; RR: relative risk; LCI: lower confidence interval; UCI: upper confidence interval; *T2 vs. T1; †T3 vs. T1.

Table 2. Prostate biopsy characteristics and associations with prostatectomy Gleason sum ≥8

Biopsy characteristics							
Candidate predictors	All patients	Prostatectomy Gleason sum		RR	95% LCI	95% UCI	*p* value
		≤7	≥8				
Median no. cores taken (IQR)	10 (10-10)	10 (10-10)	10 (10-13)	1.043	0.980	1.110	0.182
Median no. cores positive (any grade) (IQR)	5 (3-7)	5 (3-6)	6 (3-8)	1.027	0.949	1.110	0.513
Mean proportion of cores positive (any grade) (SD)	0.510 (0.263)	0.508 (0.244)	0.512 (0.292)	1.040	0.230	4.700	0.960
Highest core Gleason sum 8	24	17	7	Ref	-	-	-
Highest core Gleason sum 9	11	2	9	2.805	1.417	5.553	0.004
Highest core Gleason sum 10	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mean proportion of Gleason grade 3 from all biopsy tissue (SD)	0.049 (0.060)	0.053 (0.050)	0.046 (0.072)	0.153	<0.001	688.9	0.662
Median no. cores that contained Gleason grade 3 (IQR)	2 (1-4)	3 (2-4)	1.5 (1-3)	0.918	0.757	1.114	0.387
Mean proportion of biopsy cores that contained Gleason grade 3 (SD)	0.297 (0.218)	0.338 (0.188)	0.247 (0.245)	0.116	0.007	1.941	0.134
Highest mean proportion of Gleason grade 3 on any core (SD)	0.271 (0.203)	0.285 (0.232)	0.255 (0.168)	0.704	0.123	4.023	0.693

SD: standard deviation; IQR: interquartile range; RR: relative risk; LCI: lower confidence interval; UCI: upper confidence interval; N/A: not applicable.

not observed when at least 1 biopsy core was Gleason sum 9. In that situation almost all patients (82%) had a prostatectomy Gleason sum ≥8. Furthermore, patients with palpable tumours (higher clinical stage) were at higher risk of prostatectomy Gleason sum ≥8 compared to patients with normal prostate exams. These associations are consistent with previously published data.[12]

Given that Gleason grade 3 cancer is a component of Gleason sum ≤7, we hypothesized that patients with a large amount of Gleason grade 3 on a prostate biopsy would be more likely to have a prostatectomy Gleason sum ≤7. However, we did not observe this association in our patient cohort. The proportion of Gleason grade 3 cancer from the total biopsy tissue was not predictive of prostatectomy Gleason sum – neither the *proportion* of biopsy cores that contained Gleason 3 cancer, the *number* of cores that contained Gleason grade 3, nor the *highest proportion* of grade 3 on any one core were predictive of prostatectomy Gleason sum.

While surgical cohorts are in some ways different than radiation cohorts, we believe these findings are important to consider when counselling a patient with biopsy discordance that chooses prostate radiation. In patients with high-grade tumours, long-term androgen deprivation (2 to 3 years) has been associated with improved survival compared to short-term treatment.[13-15] Therefore, an understanding of the patient's risk of true high-grade cancer may help inform the optimal duration of androgen deprivation, and may provide the patient with a more accurate assessment of post-treatment prognosis.

There are potential limitations to these data. Several clinicians in the region performed the biopsies; therefore, there was likely variability in biopsy technique. Furthermore, the small number of patients has low statistical power to identify clinically important associations between baseline characteristics and prostatectomy Gleason sum.

Conclusion

We hypothesized that most patients with a biopsy core Gleason ≥8 and a discordant biopsy core Gleason ≤7 would have a prostatectomy Gleason sum ≥8. Our study did not support this hypothesis as only 46% patients in this cohort had a prostatectomy Gleason sum ≥8. However, if a patient

Table 3. Prostatectomy Gleason sum, pathological stage, and tumour volume

Prostatectomy characteristics			
Candidate predictors	All patients	Gleason score	
		≤7	≥8
RP Gleason score (%)			
3+3	1 (3%)	1 (5%)	0 (0%)
3+4	8 (23%)	8 (42%)	0 (0%)
4+3	10 (29%)	10 (53%)	0 (0%)
4+4	6 (17%)	0 (0%)	6 (38%)
4+5	9 (26%)	0 (0%)	9 (56%)
5+4	1 (3%)	0 (0%)	1 (6%)
Pathological stage (%)			
T2a	2 (6%)	1 (5%)	1 (6%)
T2b	1 (3%)	1 (5%)	0 (0%)
T2c	8 (23%)	4 (21%)	4 (25%)
T3a	15 (43%)	9 (47%)	6 (38%)
T3b	9 (26%)	4 (21%)	5 (31%)
Mean tumour volume (SD)*	5.5 (5.8)	4.0 (1.8)	7.5 (8.2)

*Association between tumour volume and prostatectomy Gleason sum ≥8 ($p = 0.12$). RP: radical prostatectomy; SD: standard deviation.

with discordant biopsy findings has a biopsy core with Gleason sum ≥9, he is very likely to have a prostatectomy Gleason sum ≥8. Further study to verify our findings using a larger patient cohort is warranted.

Competing interests: Dr. Heimrath, Dr. Kos, Dr. Belanger, Dr. Cagiannos, Dr. Morash, Dr. Gerridzen, Dr. Lavallée, Dr. Preston, Dr. Witiuk and Dr. Breau all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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