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Clinical Usefulness of Total Length of Gleason Pattern 4 on Biopsy in Men with Grade Group 2 Prostate Cancer

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Abstract

Purpose: To our knowledge the ideal methodology of quantifying secondary Gleason pattern 4 in men with Grade Group 2/Gleason score $3 + 4 = 7$ on biopsy remains unknown. We compared various methods of Gleason pattern 4 quantification and evaluated associations with adverse pathology findings at radical prostatectomy.

Materials and Methods: A total of 457 men with Grade Group 2 prostate cancer on biopsy subsequently underwent radical prostatectomy at our institution. Only patients with 12 or more reviewed cores were included in analysis. We evaluated 3 methods of quantifying Gleason pattern 4, including the maximum percent of Gleason pattern 4 in any single core, the overall percent of Gleason pattern 4 (Gleason pattern 4 mm/total cancer mm) and the total length of Gleason pattern 4 in mm across all cores. Adverse pathology features at radical prostatectomy were defined as Gleason score $4 + 3 = 7$ or greater (Grade Group 3 or greater), and any extraprostatic extension, seminal vesical invasion and/or lymph node metastasis. A training/test set approach and multivariable logistic regression were used to determine whether Gleason pattern 4 quantification methods could aid in predicting adverse pathology.

Results: On multivariable analysis all Gleason pattern 4 quantification methods were significantly associated with an increased risk of adverse pathology ($p < 0.0001$) and an increased AUC beyond the base model. The largest AUC increase was 0.044 for the total length of Gleason pattern 4 (AUC 0.728, 95% CI 0.663–0.793). Decision curve analysis demonstrated an increased clinical net benefit with the addition of Gleason pattern 4 quantification to the base model. The total length of Gleason pattern 4 clearly provided the largest net benefit.

Conclusions: Our findings support the inclusion of Gleason pattern 4 quantification in the pathology reports and risk prediction models of patients with Grade Group 2/Gleason score $3 + 4 = 7$ prostate cancer. The total length of Gleason pattern 4 across all cores provided the strongest benefit to predict adverse pathology features.

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Keywords

prostatic neoplasms; pathology; surgical; neoplasm grading; biopsy; risk

The GS assigned to prostate cancer biopsy specimens strongly correlates with adverse pathological features at RP, biochemical recurrence and prostate cancer specific mortality.^{1, 2} High grade cancer is associated with a worse prognosis and it impacts clinical decisions to undergo treatment. The recently adopted prognostic GrdGrp system better reflects differences among GS 7 cancers with GrdGrp 2 disease showing importantly lower posttreatment recurrence compared to that of GrdGrp 3.^{3, 4}

While risk stratification has been bolstered in recent years with the addition of tissue based biomarkers and multiparametric MRI, prostate cancer grading may be further improved with additional quantification of high grade disease. GrdGrp 2 and 3 prostate cancer is associated with a wide variation of risk and the reporting of percent of pattern 4 disease is specifically recommended in the most recent WHO genitourinary tumor classification, 4th edition.⁵ Men with favorable risk GrdGrp 2 disease may be eligible for AS under several institutional protocols.^{6–8} However, improved risk stratification is paramount, given that in the Toronto AS experience metastases developed in men with intermediate risk disease at a rate threefold higher than in men with low risk disease.⁹

In this regard several groups have reported comparable risks of disease progression in men with minimal amounts of GrdGrp 2 prostate cancer relative to GrdGrp 1.^{10, 11} Similarly it has been demonstrated that an increased proportion of GP4 prostate cancer in relation to Gleason pattern 3 is associated with an increased risk of disease specific outcomes.^{12, 13} While this relationship has been established, the clinical usefulness of these quantification metrics remains unclear. Additionally, while most series mention the overall percent of pattern 4, the ideal methodology that should be used to quantify high grade disease remains undefined.

We examined how varied methods of GP4 quantitation among men with GrdGrp 2 prostate cancer on biopsy correlate with the risk of adverse pathology at RP. We further investigated whether these metrics were clinically useful when added to standard clinicopathological parameters.

PATIENTS AND METHODS

Study Population

We identified 628 patients with highest GrdGrp 2/GS 3 + 4 = 7 prostate cancer on biopsy from July 2015 through June 2017 who subsequently underwent RP at our institution. During this time secondary GP4 quantitation was adopted as a standard component of pathology reporting at our institution in GrdGrp 2 cases. Of these men 462 had 12 or more biopsy cores reviewed and they comprised the study cohort. Slides were submitted from elsewhere for all patients with fewer than 12 cores reviewed. Five patients did not undergo lymph node dissection and were excluded from study, leaving 457 available for final analysis. We analyzed a contemporary cohort of 145 men with GrdGrp 1/GS 3 + 3 = 6

prostate cancer who underwent RP during the same period to provide a frame of reference and allow us to interpret our findings.

Composite Outcome Definitions

For our main analysis adverse pathology was defined as any of GrdGrp 3/GS 4 + 3 = 7 or higher at RP, EPE, SVI or LNM. With respect to EPE we considered that focal and established/nonfocal extension fulfilled this criterion. Sensitivity analysis was performed using a second definition of adverse pathology to include any of GrdGrp 4/GS 4 + 4 = 8 or higher, established/nonfocal EPE, SVI or LNM. This stricter definition indicating more aggressive disease was based on clinical consensus that any of these findings at RP would indicate the failure of an observational strategy if selected.

Tumor Quantification

Standard reporting of prostate biopsies at our institution since 1999 has included the percent of tissue with carcinoma and the linear amount of carcinoma in mm in each core involved by cancer. Reporting the percent of Gleason grade 4 carcinoma was standardized for GrdGrp 2 cases in 2015. All of these metrics are reported for each cancer containing core. Using these standardized reports we generated 3 methods to quantify Gleason pattern 4. 1) The overall percent of GP4 was calculated by the formula, mm of GP4 tissue (all cores)/total mm of cancer (all cores). 2) Maximum percent of GP4 refers to the single core with the greatest involvement by pattern 4. 3) We noted the sum of the total length in mm of GP4 across all cores. Individual cores were weighted equally irrespective of biopsy technique (systematic biopsy alone vs systematic plus MRI targeted cores).

Statistical Analysis

We investigated whether various GP4 quantification methods on biopsy would predict adverse pathology findings on RP using multivariable logistic regression. To assess whether GP4 quantification could aid in identifying men with low risk GS 3 + 4 = 7 disease the data set was randomly split in half to generate a training set. In this training set we tested the association between GP4 quantification and adverse pathology using multivariable logistic regression after adjusting for PSA, clinical T stage (T1 vs T2-T3), the percent of positive cores and biopsy type (systematic biopsy alone vs systematic plus MRI targeted biopsy). We then assessed the increase in discrimination after adding the GP4 quantification metrics to the base model by generating multivariable models developed in the training data set, generating predicted values from these models in the test set and calculating the AUC and 95% CI in the test set.

We also compared the clinical usefulness of the various multivariable models of interest using decision curve analysis. This method assesses the benefit of various parameters across a range of clinically relevant decision thresholds, which in this case was the predicted risk of adverse pathology at which a patient or clinician might elect treatment. All analyses were done with Stata®, version 15.

RESULTS

Among the 457 evaluable men with GrdGrp 2/GS 3 + 4 = 7 disease the risk of adverse pathology at RP was 43% (95% CI 39–48). The risk of adverse pathology among those with GrdGrp 1/GS 3 + 3 = 6 disease on biopsy during the same period was 32% (95% CI 24–40). Table 1 lists patient characteristics by RP pathology status. As expected patients with higher PSA and clinical T stage were more likely to harbor adverse pathology at RP.

Figure 1, and supplementary figures 1 and 2 (<http://jurology.com/>) show the risk of increased adverse pathology using all 3 GP4 quantification methods, including the overall percent of GP4, the maximum percent of GP4 and the total length of GP4. Patients with a limited length of GP4 disease were at a risk for adverse pathology similar to that in patients with GS 3 + 3 = 6 disease (fig. 1). Comparably men with a limited percent of GP4 also harbored adverse pathology at a rate similar to those with GS 3 + 3 = 6 disease (supplementary figs. 1 and 2, <http://jurology.com/>). On multivariable analysis all 3 GP4 quantification methods were significantly associated with an increased risk of adverse pathology (table 2).

Table 3 shows the multivariable models of interest. Models including the maximum percent of GP4, the overall percent of GP4 or the total length of GP4 resulted in an increase in the AUC with the largest increase when incorporating GP4 total length. Figure 2 shows these gains across a range of clinically relevant decision points in terms of net benefit with the addition of the 3 GP4 quantification methods to the base model.

We performed sensitivity analysis using a second definition of adverse pathology, which was GrdGrp 4/GS 4 + 4 = 8 or higher, established/nonfocal EPE, SVI or LNM. Using this more restrictive definition the risk of adverse pathology on RP among men with GrdGrp 2 disease on biopsy was 29% (95% CI 25–33) and the risk among contemporaneous patients with GrdGrp 1 disease on biopsy was 20% (95% CI 14–28). The findings of the multivariable analysis differed slightly from those of the main analysis. The maximum percent of GP4 in any single core was no longer significantly associated with adverse pathology ($p = 0.3$, supplementary table 1, <http://jurology.com/>). All AUCs increased meaningfully when adding the GP4 quantification methods to the base model with the largest increase again occurring when incorporating the total length of GP4 in mm (supplementary table 2, <http://jurology.com/>). On decision curve analysis we observed the maximal gain in terms of net benefit with the addition of total GP4 length to the base model (supplementary fig. 3, <http://jurology.com/>).

DISCUSSION

We studied 3 methods of quantitative Gleason grading on biopsy and observed that total GP4 length best predicted adverse pathology findings at RP among men with GrdGrp2 prostate cancer. By all quantification metrics (maximum and overall GP4 percent, and total length) as the amount of GP4 increased, the risk of adverse pathology increased as well. On decision curve analysis incorporating total GP4 length resulted in the greatest gains above our base model analysis across a range of clinically relevant threshold probabilities. For example, if a

patient or clinician elected treatment when faced with a 50% risk of adverse pathology, the model incorporating total GP4 length would confer the greatest net benefit at this threshold.

Considering the heterogeneity of intermediate risk prostate cancer, our findings are important, given the potential impact on eligibility for AS, which guidelines support in select individuals with GrdGrp2 disease.^{14–16} Improved risk stratification in this intermediate risk group is valuable due to the substantially increased risk of progression on surveillance compared to that in men with low risk disease.⁹

Our main analysis was performed with a conservative definition of adverse pathology. This first definition, GS 4 + 3 = 7 or greater, any EPE, SVI or LNM, is in keeping with several other publications in the field.^{12, 13, 17} Using this definition most cases of adverse pathology were due to a finding of EPE. Given that some data have shown that focal EPE may not portend a particularly adverse prognosis,^{18, 19} we performed sensitivity analysis with a second, more restrictive definition of GS 4 + 4 = 8 or greater, established/nonfocal EPE, SVI or LNM. When faced with a theoretical patient with favorable GrdGrp 2 disease considering active surveillance, there would be a failure of risk stratification when meeting any of these stricter pathological criteria if he selected RP. While this second definition was satisfied in 29% of cases compared to 43% using the first definition, we observed findings similar to those of the main analysis, in that GP4 total length still outperformed the other quantification methods.

Groups at several institutions have previously reported quantitative Gleason grading of biopsy specimens. A group from the University of Michigan evaluated 1,691 men who underwent RP during 2005 to 2013.¹² Overall the percent of GP4 demonstrated better performance characteristics than the maximum percent of GP4 and it was used for all analyses. The investigators reported a low risk of adverse pathology (primary Gleason pattern 4, or pT3 or greater) in men with less than 20% GP4, possibly representing a threshold. Furthermore, on multivariable analysis the percent of GP4 was significantly associated with time to biochemical recurrence (HR 1.02, 95% CI 1.01–1.02).

Experience at a large German center echoed these findings, in which the overall percent of GP4 on biopsy was dichotomized as 3 + 4 low (less than 25% GP4) and 3 + 4 high (25% to 49% GP4).²⁰ We also report an increased adverse pathology rate with an increasing percent of GP4 but found that the overall and maximum percent models performed similarly.

In a more recent series Perlis et al incorporated the overall percent of GP4 on biopsy with standard clinicopathological parameters on multivariable analysis to examine its usefulness in 1,255 patients with GrdGrp2 prostate cancer.¹³ For each percent increase in pattern 4 tissue they observed 2% higher odds of nonorgan confined disease. The percent of Gleason pattern 4 became less important to predict adverse pathology in men with PSA less than 8 ng/ml and a total amount of all cancer of less than 15%. These findings were described as a limitation of GP4 quantification, in that the men were likely at lower risk, might be directed to AS and could potentially benefit from improved risk stratification. This contrasts with our decision curve analysis, which demonstrated clinical usefulness for all 3 quantification methods above our base model over a range of relevant thresholds. Furthermore, the

maximum percent of GP4 (a single core with the highest percent) is an easily identifiable metric without any calculation. We found that it performed similarly to the overall percent of GP4 but it was not available for analysis in the study by Perlis et al.¹³

GP4 quantification was uniformly adopted into synoptic pathology reporting in mid 2015 at our institution. Thus, followup in this cohort was limited. Longer term data are required on biochemical recurrence, metastasis and prostate cancer specific mortality. However, our composite definition of adverse pathology likely represents an adequate surrogate end point for this study. While accurate prediction of Gleason upgrading or nonorgan confined disease at RP would likely alter the clinical decision to pursue AS, the absence of adverse pathology alone is not synonymous with appropriateness for surveillance.

Readers may question the fact that our main adverse pathology end point was met in a third of the men with GS 3 + 3 = 6 disease who underwent RP during the study period. Importantly this group comprised highly select men who were directed to surgery in the contemporary era based on disease volume, imaging and/or biomarker findings. We acknowledge that this comparator group may not represent the typical patient with very low risk disease who is enrolled on active surveillance.

Finally, we are limited in that we did not incorporate additional risk stratification tools into our base model, such as the PIRADS™ (Prostate Imaging-Reporting and Data System) score on MRI or tissue biomarkers. While these tools are increasingly used to aid decision making in cases of localized prostate cancer, they have not been uniformly adopted.

Our study has several unique strengths. Standardized reporting by dedicated genitourinary pathologists during the inclusion period allowed us to generate the 3 quantification methods which we used. Also, our cohort reflects contemporary diagnostic pathways incorporating MRI targeted biopsy. Approximately half of our cohort had MRI targeted cores in addition to a systematic template and adjustment for biopsy strategy was incorporated into our models. Recognizing the extensive referral and second opinion practice at our pathology department, only in house biopsies and outside cases in which 12 or more cores were reviewed were included in analysis. It is common practice for our pathology department to be sent a select few cores to rereview and we chose to exclude these cases to minimize potential bias.

Finally, we incorporated decision curve analysis to evaluate the usefulness of the various predictive models. This technique evaluates the net benefit of the models across a range of risk thresholds at which a patient might elect treatment, further clarifying clinical usefulness beyond typically reported metrics such as the AUC.²¹

We found that quantitative Gleason grading on prostate biopsy, particularly with the total length of GP4, adds clinical utility above standard clinicopathological parameters and bolsters decision making in men with GrdGrp 2 prostate cancer. This has important implications when selecting candidates for AS vs upfront radical therapy. Extracting useful information from existing pathological data represents an elegant and low cost intervention. Further work directed at validating these findings and integrating them with biomarker and imaging data is warranted.

CONCLUSIONS

Our findings support the inclusion of Gleason pattern 4 quantification in pathological reporting and risk prediction models in patients with GrdGrp 2/GS 3 + 4 = 7 prostate cancer. The total length of GP4 across all cores, a metric typically neither included nor calculated, provides the strongest benefit to predict adverse pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

AS	active surveillance
EPE	extraprostatic extension
GP4	Gleason pattern 4
GrdGrp	Grade Group
GS	Gleason score
LNM	lymph node metastasis
MRI	magnetic resonance imaging
RP	radical prostatectomy
SVI	seminal vesicle invasion

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Figure 1.

Risk of adverse pathology by total length of GP4 in mm estimated by Epanechnikov kernel weighted local polynomial regression. Shaded region represents GP4 total length distribution. Horizontal line indicates risk of adverse pathology in contemporaneous GrdGrp1/GS 3 + 3 = 6 cohort, which was not estimated for values above 12 mm due to small number of adverse pathology events in that range.

Figure 2.

Decision curve analysis shows added benefit of GP4 quantification in addition to base model (dashed gray curve) to detect adverse pathology in test set. Clinical net benefit is plotted against risk threshold at which patient or clinician would elect treatment. Horizontal line represents GP4 total length. Gray curve represents overall GP4 percent. Dashed black curve represents maximum GP4 percent.

Table 1.

Patient characteristics by radical prostatectomy pathology features

	Radical Prostatectomy Adverse Pathology		p Value *
	No	Yes	
No. pts (%)	259 (57)	198 (43)	–
Median age at biopsy (95% IQR)	61 (56–66)	62 (57–66)	0.2
Biopsy type:			
Systematic	132 (51)	117 (59)	0.089
MRI targeted	127 (49)	81 (41)	
Median No. biopsy cores (95% IQR)	14 (12–16)	14 (12–16)	0.14
Total ng/ml preop PSA (95% IQR)	5.7 (4.2–7.5)	6.6 (4.7–9.6)	0.001
No. clinical stage (%):			
T1	203 (78)	126 (64)	0.0005
T2-T3	55 (21)	72 (36)	
Unknown	1 (0.4)	0	
No. extraprostatic extension (%):			–
Nonfocal/established	–	120 (61)	
Focal	–	56 (28)	
Organ confined	259 (100)	22 (11)	
No. seminal vesical invasion (%):	–	27 (14)	–
No. lymph node metastasis (%):	–		–
Known		26 (13)	
Unknown		2 (1.0)	
No. primary radical prostatectomy Gleason pattern (%):			–
3	259 (100)	138 (70)	
4	–	60 (30)	

* Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables.

Table 2.

Multivariable logistic regression models testing association of variable of interest with adverse pathology risk in patients with Grade Group 2/Gleason score 3 + 4 = 7 disease on biopsy, regressed and tested in training set

Gleason Pattern 4	OR (95% CI)	p Value
Max %/1% increase	1.02 (1.00–1.05)	0.049
Overall %/1% increase	1.06 (1.03–1.10)	0.001
Total length	1.33 (1.11–1.58)	0.002

Model covariates included PSA, clinical stage (T1 vs T2-T3), percent of positive cores and MRI targeted biopsy status.

Table 3.

Test set AUCs based on multivariable models generated in training set in patients with Grade Group 2/Gleason score 3 + 4 = 7 disease on biopsy

Model	AUC (95% CI)
Base *	0.684 (0.615–0.752)
Base + max % Gleason pattern 4	0.719 (0.652–0.785)
Base + overall % Gleason pattern 4	0.697 (0.629–0.765)
Base + total length Gleason pattern 4	0.728 (0.663–0.793)

* PSA, clinical stage (T1 vs T2-T3), percent of positive cores and MRI targeted biopsy status.