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Upgrading and Downgrading of Prostate Needle Biopsies: Risk Factors and Clinical Implications

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Abstract

Background—The prostate biopsy Gleason grade frequently differs from the radical prostatectomy (RP) grade. Given the critical role needle biopsy plays in treatment decisions, we determined risk factors for upgrading and downgrading the prostate biopsy.

Methods—We determined the significant predictors of upgrading (higher RP grade than biopsy grade) and downgrading (lower RP grade than biopsy grade) among 1,113 men treated with RP between 1996 and 2005 within the SEARCH Database who underwent at least a sextant biopsy. Gleason sum was examined as a categorical variable of 2–6, 3+4, and ≥4+3.

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Results—Overall, 299 men (27%) were upgraded, 123 (11%) were downgraded, and 691 (62%) had identical biopsy and pathological Gleason sum groups. Upgrading was associated with adverse pathology ($p \leq 0.001$) and risk of biochemical progression ($p = 0.001$) while downgrading was associated more favorable pathology ($p \leq 0.01$) and a decreased risk of progression ($p = 0.04$). On multivariable analysis, higher PSA ($p < 0.001$), more biopsy cores with cancer ($p = 0.001$), and obesity ($p = 0.003$) were all significantly positively associated with upgrading while biopsy Gleason sum 3+4 ($p = 0.001$) and obtaining ≥ 8 biopsy cores ($p = 0.01$) were associated with less likelihood of upgrading.

Conclusions—Men who were upgraded were at greater risk of adverse pathology and biochemical progression. Men with “high-risk” cancer (higher PSA, more cores positive and obese) were more likely to be upgraded while obtaining more biopsy cores reduced the likelihood of upgrading.

Keywords

Prostate cancer; radical prostatectomy; Gleason; prostate biopsy; obesity

INTRODUCTION

Biopsy and radical prostatectomy (RP) Gleason sums only match in 45% of cases.^{1–3} This likely results from intra- and inter-observer variability in Gleason grading,⁴ and sampling error with the biopsy. If factors can be identified which predict upgrading and downgrading, these factors could be used to help determine how reliable the biopsy Gleason sum is in predicting the cancer’s biological potential. We used the large multi-center multi-ethnic Shared Equal Access Regional Cancer Hospital (SEARCH) Database⁵ to determine the accuracy of biopsy Gleason sum to predict RP Gleason sum and identify risk factors for upgrading and downgrading.

MATERIALS AND METHODS

Study population

After obtaining Institutional Review Board approval from each institution to abstract and combine data, data from patients undergoing RP at the Veterans Affairs Medical Centers in West Los Angeles, Palo Alto, San Francisco, and Augusta, and the San Diego Naval Hospital were combined into the SEARCH database.⁵ Patients treated with preoperative androgen deprivation or radiation therapy were excluded. Because we sought to evaluate the association between extended biopsy schemes, which were not introduced at our centers until 1996, and risk of upgrading and downgrading, we limited our potential patient population to men treated in 1996 or later. We excluded 19 men diagnosed from a transurethral resection as this affects PSA; 12 and 10 with missing biopsy and pathological Gleason data, respectively; and 63 and 67 with unknown or < 6 biopsy cores obtained, respectively, resulting in a study population of 1,113. Excluded men were older, treated in earlier years, had higher clinical stage, and higher PSA values. Of the 1,090 men with follow-up data available (mean and median follow-up of 47 and 36 months; range: 1–185 months), 212 (19%) experienced biochemical progression, defined as a single PSA > 0.2 ng/ml, 2 concentrations at 0.2 ng/ml, or secondary treatment for an elevated postoperative PSA.

The protocol for processing RP specimens was similar across sites with 4 of 5 using step sectioning with 3 to 5 mm intervals and embedding all sections for analysis. The 5th center used representative sections of the apex, base, inferior, mid, and superior aspects of the gland, including any grossly evident tumor, and seminal vesicles as per the protocol outlined by experienced academic genitourinary pathologists.⁶

Statistical analysis

Men were grouped by Gleason sum: 2–6, 3+4=7, and $\geq 4+3$. Upgrading was considered RP grade in a higher category than the biopsy and downgrading was considered RP grade in a lower group than the biopsy. The significant independent predictors of upgrading and downgrading were determined using logistic regression. For determining predictors of upgrading, men with biopsy Gleason $\geq 4+3$ were excluded as they could not be upgraded from the highest category. Likewise men in the lowest category (Gleason 2–6) were excluded for determining downgrading predictors. Multivariable analysis was performed using a backwards stepwise selection with the variable with the highest p value successively deleted until only variables with a $p < 0.1$ remained. The variables considered for entry included biopsy Gleason sum, PSA (continuous after logarithmic transformation), age at RP (continuous), year of RP (continuous), number of biopsy cores with cancer (continuous), number of biopsy cores obtained (≥ 8 vs. < 8 cores), clinical stage (T2/3 vs. T1), race (black, nonblack-nonwhite vs. white), body mass index (BMI; kg/m^2 : 25.0–29.9, ≥ 30.0 vs. < 25.0), and height (tertiles).

The odds ratio (OR) and relative risk (RR) of adverse pathological features and time to biochemical progression for upgraded and downgraded men were examined using logistic regression analysis and Cox proportional hazards analysis, respectively, adjusting for the clinical covariates of PSA, age at RP, year of RP, biopsy Gleason, number of biopsy cores with cancer, number of biopsy cores obtained, clinical stage, race, BMI, and height.

The distribution of all clinical and pathological variables was similar among the SEARCH sites. Therefore, data from all centers were combined for analyses.

RESULTS

Most patients were white, had biopsy and RP Gleason sums 2–6, PSA < 10 ng/ml, and pathologically organ-confined disease (table 1). 299 men (27%) were upgraded, 123 (11%) were downgraded, and 691 (62%) had identical biopsy and pathological Gleason groups (table 2).

After adjusting for multiple clinical covariates, upgraded men were more likely to have positive surgical margins (OR 2.34, 95% CI 1.69–3.26, $p < 0.001$), extracapsular extension (OR 3.29, 95% CI 2.24–4.84, $p < 0.001$), and seminal vesicle invasion (OR 3.87, 95% CI 1.74–8.62, $p = 0.001$). Downgraded men were less likely to have extracapsular extension (OR 0.36, 95% CI 0.20–0.65, $p = 0.001$) and seminal vesicle invasion (OR 0.28, 95% CI 0.10–0.76, $p = 0.01$). There was no significant association between downgrading and positive surgical margins (OR 0.67, 95% CI 0.40–1.14, $p = 0.14$).

After adjusting for clinical covariates, upgrading was associated with increased risk of biochemical progression (RR 1.86, 95% CI 1.30–2.64, $p = 0.001$, figure 1) and downgrading was associated with decreased risk of progression (RR 0.61, 95% CI 0.39–0.97, $p = 0.04$, figure 2).

On multivariable analysis, higher PSA, more biopsy cores with cancer, and obesity were associated with upgrading while biopsy Gleason sum 3+4 and obtaining ≥ 8 biopsy cores were inversely associated with upgrading (table 3). There was a trend, which did not reach statistical significance, for overweight ($p = 0.06$) and recent year of surgery ($p = 0.06$) to be associated with upgrading. On multivariable analysis, obtaining ≥ 8 biopsy cores was associated with downgrading. Higher PSA and recent year of surgery were inversely associated with downgrading.

DISCUSSION

In a multicenter study of over 1,100 men we found that the biopsy and RP Gleason groups matched in 62% of cases. Upgraded men were more likely to have adverse pathology and biochemical progression. Factors known to correlate with aggressive cancers (e.g. more cores with cancer, higher PSA, obesity) were associated with upgrading while factors associated with less aggressive cancers (e.g. lower PSA) were associated with downgrading. Obtaining more biopsy cores was associated with reduced likelihood of upgrading and increased likelihood of downgrading.

When grouped into clinically meaningful categories, biopsy and RP Gleason sums match in 65% of cases,² in line with the 62% in the current study. Of the mismatched biopsy and RP grades in the current study, most (27%) were upgraded and relatively few were downgraded (11%): similar to the findings of King,⁷ who summarized data from multiple studies showing an exact match rate of 42% and an upgrading rate of 43%. The one exception to the generalization that biopsy Gleason often matches or underestimates RP grade was men with biopsy Gleason $\geq 4+3$ in whom $>40\%$ were downgraded; analogous again to the findings of King.⁷

The clinical importance of upgrading is dramatic, particularly for men with biopsy Gleason 6 who choose radiation therapy. If it were known before treatment that the patient had Gleason 7, this might affect the type and/or location of radiation and the possible addition of hormonal therapy. Indeed, in the current and in a prior study,⁸ upgraded men were more likely to have adverse pathology and biochemical progression supporting the more aggressive nature of upgraded cancers.

Of the few studies that examined predictors of upgrading, several suggested that small volume cancers on biopsy (e.g. <3 mm) is a risk factor for upgrading,^{1,9} though others found no association between biopsy cancer volume and upgrading.^{3,7,10} Most of these studies were limited by the small patient numbers often totaling 300 or fewer, limiting the statistical power to detect clinically important associations. In the current study of $>1,100$ men, we identified that more biopsy cores with cancer, higher PSA, and obesity, which all correlate with more aggressive cancers, all predicted upgrading.

Over the past 5–10 years, extended biopsy schemes have become common due to their increase in cancer detection.¹¹ Prior studies found obtaining more cores increased the concordance between biopsy and RP Gleason sums.^{3,12,13} Similarly, we found obtaining ≥ 8 cores reduced the risk of upgrading. Therefore, in men diagnosed based upon a sextant biopsy and in whom the biopsy Gleason sum would influence the treatment approach (e.g. radiation therapy or expectant management), consideration should be given to repeating a sextant biopsy to ensure grading accuracy.

Obese men were more likely to be upgraded. Obesity is associated with increased risk of high-grade disease in the RP^{14,15} and prostate cancer death.¹⁶ This increased upgrading risk may also explain, at least in part, why when adjusting for only pre-operative clinical characteristics, obese men are at increased risk for biochemical progression after RP.^{14,15} While the reasons underlying the selective upgrading in obese men are unclear, obese men have larger sized prostates,¹⁷ which may have contributed to poorer sampling on biopsy among obese men. Unfortunately, due to the fact that ultrasound prostate volume was not available on the vast majority of men, we are unable to test this hypothesis. However, regardless of the reasons behind this selective upgrading, the clinical implication is that despite low-grade cancer on biopsy, obese men are more likely to harbor high-grade disease.

Over time, there has been a shift toward assigning higher Gleason grades due to differing pathological interpretation.¹⁸ However, the short time interval between biopsy and RP for most patients results in the biopsy and RP being read in the same era. Therefore, long-term trends in Gleason grading are unlikely to have influenced our results. Also, we limited our analysis to men treated since 1996. Although studies suggested that post-operative PSA doubling time may be a better end-point than PSA progression,¹⁹ PSA doubling times were not available in the SEARCH Database. Pre-operative prostate ultrasound volumes which may affect sampling error and thus be predictive of upgrading and downgrading were not available on the majority of our patients. The current study used non-centralized pathologic evaluation of surgical specimens from multiple institutions by multiple pathologists, which may make pooling of pathologic findings problematic. However, the same pathology department read both the biopsy and RP at each center. Moreover, the protocol for processing the RP specimens, as outlined above, was extremely thorough at all centers. Finally, given the large number of prostate biopsy performed annually in the United States, it is impossible for dedicated genitourinary pathologists to read all biopsy slides. Therefore, many if not most prostate biopsies are read by community pathologists and as such, our pathologic data which represents pooling of data from multiple pathologists across multiple institutions may better represent what most practicing urologists can expect in their own practice.

CONCLUSIONS

In the current study, biopsy and RP Gleason sums matched in 62% of cases. Upgraded men were had more advanced disease and greater risk of biochemical progression. Men with “high-risk” cancer were at increased risk of upgrading, while men with “low-risk” cancers were at increased risk for downgrading. Obtaining more biopsy cores improved the accuracy of the biopsy Gleason to predict pathological Gleason sum.

References

1. Bostwick DG. Gleason grading of prostatic needle biopsies. Correlation with grade in 316 matched prostatectomies. *Am J Surg Pathol.* 1994; 18:796–803. [PubMed: 8037294]
2. Steinberg DM, Sauvageot J, Piantadosi S, Epstein JI. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. *Am J Surg Pathol.* 1997; 21:566–76. [PubMed: 9158682]
3. King CR, McNeal JE, Gill H, Presti JC Jr. Extended prostate biopsy scheme improves reliability of Gleason grading: implications for radiotherapy patients. *Int J Radiat Oncol Biol Phys.* 2004; 59:386–91. [PubMed: 15145152]
4. Ozdamar SO, Sarikaya S, Yildiz L, Atilla MK, Kandemir B, Yildiz S. Intraobserver and interobserver reproducibility of WHO and Gleason histologic grading systems in prostatic adenocarcinomas. *Int Urol Nephrol.* 1996; 28:73–7. [PubMed: 8738623]
5. Freedland SJ, Amling CL, Dorey F, Kane CJ, Presti JC, Terris MK, Aronson WJ. Race as an outcome predictor after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. *Urology.* 2002; 60:670–4. [PubMed: 12385931]
6. Hall GS, Kramer CE, Epstein JI. Evaluation of radical prostatectomy specimens. A comparative analysis of sampling methods. *Am J Surg Pathol.* 1992; 16:315–24. [PubMed: 1373577]
7. King CR. Patterns of prostate cancer biopsy grading: trends and clinical implications. *Int J Cancer.* 2000; 90:305–11. [PubMed: 11180133]
8. Sved PD, Gomez P, Manoharan M, Kim SS, Soloway MS. Limitations of biopsy Gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer. *J Urol.* 2004; 172:98–102. [PubMed: 15201746]
9. Fukagai T, Namiki T, Namiki H, Carlile RG, Shimada M, Yoshida H. Discrepancies between Gleason scores of needle biopsy and radical prostatectomy specimens. *Pathol Int.* 2001; 51:364–70. [PubMed: 11422794]

10. Carlson GD, Calvanese CB, Kahane H, Epstein JI. Accuracy of biopsy Gleason scores from a large uropathology laboratory: use of a diagnostic protocol to minimize observer variability. *Urology*. 1998; 51:525–9. [PubMed: 9586600]
11. Presti JC Jr, Chang JJ, Bhargava V, Shinohara K. The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: results of a prospective clinical trial. *J Urol*. 2000; 163:163–6. [PubMed: 10604337]
12. Makhoulf AA, Krupski TL, Kunkle D, Theodorescu D. The effect of sampling more cores on the predictive accuracy of pathological grade and tumour distribution in the prostate biopsy. *BJU Int*. 2004; 93:271–4. [PubMed: 14764121]
13. Coogan CL, Latchamsetty KC, Greenfield J, Corman JM, Lynch B, Porter CR. Increasing the number of biopsy cores improves the concordance of biopsy Gleason score to prostatectomy Gleason score. *BJU Int*. 2005; 96:324–7. [PubMed: 16042723]
14. Freedland SJ, Aronson WJ, Kane CJ, Presti JC Jr, Amling CL, Elashoff D, Terris MK. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. *J Clin Oncol*. 2004; 22:446–53. [PubMed: 14691122]
15. Amling CL, Riffenburgh RH, Sun L, Moul JW, Lance RS, Kusuda L, Sexton WJ, Soderdahl DW, Donahue TF, Foley JP, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J Clin Oncol*. 2004; 22:439–45. [PubMed: 14691120]
16. Rodriguez C, Patel AV, Calle EE, Jacobs EJ, Chao A, Thun MJ. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:345–53. [PubMed: 11319175]
17. Freedland SJ, Platz EA, Presti JC Jr, Aronson WJ, Amling CL, Kane CJ, Terris MK. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. *J Urol*. 2006; 175:500–4. [PubMed: 16406980]
18. Albertsen PC, Hanley JA, Barrows GH, Penson DF, Kowalczyk PD, Sanders MM, Fine J. Prostate cancer and the Will Rogers phenomenon. *J Natl Cancer Inst*. 2005; 97:1248–53. [PubMed: 16145045]
19. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst*. 2003; 95:1376–83. [PubMed: 13130113]

Figure 1. Actuarial 6-year Kaplan-Meier estimates of biochemical recurrence rates of patients with biopsy Gleason sum $\leq 3+4$ cancers treated with radical prostatectomy segregated by whether the Gleason sum was upgraded from biopsy to radical prostatectomy specimen (log-rank, $p < 0.001$).

Figure 2.

Actuarial 6-year Kaplan-Meier estimates of biochemical recurrence rates of patients with biopsy Gleason sum $\geq 3+4$ cancers treated with radical prostatectomy segregated by whether the Gleason sum was upgraded from biopsy to radical prostatectomy specimen (log-rank, $p=0.06$).

TABLE 1

Pre-operative clinical and pathological characteristics of men undergoing radical prostatectomy

No. patients	1,113
Mean age $\pm$ SD (yr)	60.6 $\pm$ 6.5
Race	
White	624 (56)
Black	347 (31)
Nonblack-nonwhite	135 (12)
PSA (ng/ml)	
Mean $\pm$ SD	8.3 $\pm$ 7.4
Median	6.4
No. biopsy Gleason sum (%)	
2–6	752 (68)
3+4	216 (19)
$\geq 4+3$	145 (13)
No. biopsy cores obtained	
<8	304 (27)
≥ 8	809 (73)
median	10
mean (range)	10.6 (6–40)
No. positive cores	
median	2
mean (range)	2.8 (1–12)
Body mass index (kg/m ²)	
< 25.0	268 (25)
25.0 – 29.9	517 (48)
30.0 – 34.9	198 (19)
≥ 35.0	86 (8)
No. clinical stage (%)	
T1	639 (58)
T2/T3	460 (42)
No. pathological Gleason sum (%)	
2–6	589 (53)
3+4	321 (29)
$\geq 4+3$	203 (18)
No. positive surgical margins (%)	351 (32)
No. extracapsular extension (%)	260 (24)
No. seminal vesicle invasion (%)	70 (6)
No. positive lymph nodes (%)	9 (1)

Table 2

Association between biopsy and RP specimen Gleason sum among men in the SEARCH Database

	Biopsy Gleason sum		
	2–6	3+4	≥4+3
Pathological Gleason sum			
2–6	508 (68)	64 (30)	17 (12)
3+4	182 (24)	97 (45)	42 (29)
≥4+3	62 (8)	55 (25)	86 (59)

TABLE 3

Multivariable logistic regression analysis of factors predicting Gleason sum upgrading and downgrading from biopsy to radical prostatectomy specimen among men in the SEARCH Database

	Odds Ratio	95% CI	P Value
Predictors of upgrading			
Serum PSA	1.91	1.48 – 2.47	<0.001
Biopsy Gleason sum (3+4 vs. 2–6)	0.51	0.34 – 0.75	0.001
No. of biopsy cores with cancer	1.13	1.04 – 1.22	0.002
Body mass index (≥ 30 vs. <25 kg/m ²)	1.89	1.24 – 2.87	0.003
No. of biopsy cores obtained (≥ 8 vs. <8)	0.62	0.43 – 0.89	0.01
Year of surgery	1.07	1.00 – 1.14	0.06
Body mass index (≥ 25 – <30 vs. <25 kg/m ²)	1.44	0.99 – 2.11	0.06
Predictors of downgrading			
No. of biopsy cores obtained (≥ 8 vs. <8)	3.16	1.63 – 6.14	0.001
Serum PSA	0.53	0.34 – 0.81	0.003
Year of surgery	0.88	0.80 – 0.98	0.02