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Factors associated with downgrading in patients with high grade prostate cancer

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Abstract

Objective: To determine the factors associated with downgrading between biopsy and prostatectomy in the contemporary era using extended-template biopsy techniques.

Materials and methods: The UCSF Urologic Oncology Database was used to identify subjects diagnosed with high grade prostate cancer (primary pattern 4 or 5) in at least one core on extended-pattern biopsy. Multivariable logistic regression analysis was performed to identify independent factors associated with downgrading at radical prostatectomy, defined as a change from primary pattern 4 or 5 to primary pattern 3.

Results: Downgrading occurred in 68 (34%) of 202 subjects who met the study criteria. Fourteen (47%) of 30 subjects with ≤25% of cores that were high grade and 9 (43%) of 21 subjects with <10% of total tissue containing cancer were downgraded. In a multivariable model, patients with mixed grade cores had much higher odds of downgrading than those with all high grade cores (OR 3.0 95% 1.3–7.1), $P < 0.01$). The proportion (per 10% increment) of positive cores containing high grade cancer (OR 0.8 95% CI 0.7–0.9 $P < 0.01$) and the percent (per 10% increment) of total tissue containing cancer (OR 0.7 95% CI 0.6–0.9 $P = 0.01$) were significantly associated with lower odds of downgrading.

Conclusions: Downgrading following radical prostatectomy is a common event. Biopsy over-grading may preclude men from active surveillance or lead to unnecessary lymphadenectomy, excess radiation, or prolonged hormone therapy. The proportion of positive biopsy cores that are high grade and the percent of total tissue containing cancer should be incorporated into decision making.

Keywords: Prostatic neoplasms; Biopsy; Gleason score; Tumor staging

1. Introduction

In 2010, prostate cancer was diagnosed in approximately 220,000 men and caused 32,000 deaths [1]. Clinical and demographic characteristics such as patient age, comorbidities [2], prostate specific antigen (PSA) level, clinical stage, and biopsy Gleason score are important factors in guiding nuanced treatment decisions—eligibility for active surveillance, need for lymphadenectomy at prostatectomy, and duration of androgen deprivation with radiation to name a few [3,4]. In the PSA-screening era, in which most men are diagnosed with low PSA and low stage disease, the biopsy Gleason score is a critical factor in risk assessment; therefore, over-grading may lead to over-treatment [5]. Unfortunately, the agreement between biopsy and prostatectomy Gleason score is only modest [6]. This is likely caused by within-patient grade heterogeneity and/or sampling error [7].

The impact of both may be lessened by the use of extended biopsy patterns, which are now the standard of care [8]. However, discrepancies between biopsy and prostatectomy Gleason score still persist, probably due to the

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biopsy grade being based on the highest grade core while pathologic grade represents the most common grade found. Risk stratification tools, in turn, are based on the highest Gleason score on biopsy, giving the same weight to 1% and to 100% of cores that are high grade [9]. Several studies in the pre-PSA or early PSA era have shown better correlation between percent of patterns 4 or 5 on biopsy and prostatectomy Gleason scores than biopsy Gleason total [10,11]. These findings have been confirmed in a multivariable model using sextant biopsies [12], as well as extended pattern biopsies, but only in univariable analysis [13]. In addition, a small study of patients with a single core with a micro-focus of high grade disease found very high rates of downgrading, suggesting that the percent of total tissue with cancer may be a significant factor [14].

The aim of this study was to determine the factors associated with downgrading following RP in the modern PSA era, using extended pattern biopsy techniques controlling for important clinical and demographic characteristics.

2. Patients and methods

Men who underwent RP within 6 months after the first positive biopsy for prostate cancer were identified through the UCSF Urologic Oncology Database. All patients provided written, informed consent to collect clinical, pathologic, and follow-up information in accordance with approval by the Institutional Review Board. Inclusion criteria were high grade prostate cancer identified on a ≥10 core biopsy (extended pattern biopsy) [15]. High grade disease was defined as primary pattern 4 or 5 in any single core; therefore, patients with 4+3 and 8–10 were included. Exclusion criteria were any form of neoadjuvant treatment prior to prostatectomy.

All prostate specimens were weighed, fixed, inked, and sectioned at 3–4 mm intervals perpendicular to the urethral axis according to standard institutional protocol. Biopsy and RP specimens were assessed by pathologists who focus on genitourinary pathology, and all biopsies performed at outside institutions were reviewed at UCSF. Biopsies were reported with a primary (most common) and secondary (highest) Gleason pattern, while prostatectomies were reported with a primary (most common), and secondary (second most common) Gleason pattern [16]. Although a tertiary pattern was recorded when present, it was not included in the analysis since most risk stratification schemes only incorporate the primary and secondary patterns.

Mixed grade cores were defined in patients with both high (4+3 or 8–10) and low/intermediate (3+3 or 3+4) grade cores. Percent of cores positive was computed as the number of positive cores over the number of cores taken. Percent of positive cores with high grade was defined as the number of cores with high grade (4+3 or 8–10) divided by the total number of positive cores. The length of tissue taken (in mm) and length of tissue positive (in mm) were reported for each core. Methods similar to those for grade were used to calculate percentages of total tissue taken (mm) of individual cores. Demographic, clinical, and pathologic characteristics of the groups were compared using χ^2 for categorical and *t*-test for continuous variables. Pearson's r was used to assess correlation between continuous clinical and mapped biopsy characteristics.

The primary endpoint was defined as downgrading at prostatectomy from primary patterns 4 or 5 to primary pattern 3 (including 3+4). High grade tertiary patterns were not included in the analysis. Logistic regression was used to determine the independent association of clinical and demographic variables with downgrading. The first model included diagnostic age, year, and clinical characteristics (PSA, prostate volume on TRUS, clinical stage, biopsy source, Gleason score, and presence of mixed grade cores). The second model included mapped biopsy details (number of cores taken, percent of cores positive, proportion of positive cores with high grade, total tissue taken, percent tissue positive, and proportion of cancer tissue which was Gleason pattern 4–5). All cores and tissue detail variables were included a priori, despite inter-variable correlations. The final model included both the set of age and clinical risk variables and the mapped biopsy details. Forward stepwise selection was used to retain only those covariates that were independently associated with downgrading (based on a P value < 0.05). All statistical analyses were performed using SAS 9.1 for Windows (SAS Institute, Cary, NC).

3. Results

Between 1995 and 2009 (median 2006), 202 patients who underwent prostatectomy within 6 months of 10-core biopsy and had at least one high grade core, were included in the analysis. The median age at diagnosis was 61.0 years (range 45–77 years) and median PSA was 6.8 ng/mL (range 0.1–154 mL). All but 2 subjects had clinical stage T1 or T2. Maximum Gleason biopsy score was 7 (4+3) in 54 (27%) and 8–10 in 148 (73%).

Downgrading occurred in 68 (34%) patients. Fourteen (47%) of 30 subjects with ≤25% of cores high grade and 9 (43%) of 21 subjects with <10% of total tissue containing cancer were downgraded. A detailed comparison between those who were and were not downgraded is illustrated in Table 1. Tertiary grade was present 34 patients (17%), Gleason 3 in 8 (24%), Gleason 4 in 1 (3%), and Gleason 5 in 25 (73%). On univariate analyses, those who were downgraded tended to have a lower PSA (6.4 vs. 7.1, $P = 0.05$). Downgrading was less common in those men with a higher proportion of mixed (high and low grade) cores (82% vs. 60%, $P < 0.01$) and lower proportion of positive cores with high grade cancer (50% vs. 79%, $P < 0.01$). In addition, downgraded patients had a lower percent of total biopsy tissue with cancer (23% vs. 27%, $P < 0.01$) and a lower percent of high grade cancer (64% vs. 93%, $P < 0.01$).

Table 1
Baseline characteristics in subjects with mixed and homogenous Gleason scores on diagnostic prostate biopsy

Characteristic	Low and high grade primary (n = 136)		Only high grade primary (n = 66)		
	No. patients	(%)	No. patients	(%)	P value
Age (years)					0.57
>55	22	(16)	6	(9)	
55–59	31	(23)	17	(26)	
60–64	45	(33)	22	(33)	
≥65	38	(28)	21	(32)	
Year of diagnosis	136		66		0.75
≤2003	28	(21)	14	(21)	
2004–2006	35	(26)	20	(30)	
2007–2009	73	(54)	32	(48)	
Biopsy at UCSF					0.35
No	90	(66)	48	(72)	
Yes	46	(34)	18	(27)	
PSA (ng/ml)					0.38
≤4 ng/ml	16	(12)	6	(9)	
4.1–6	36	(26)	21	(32)	
6.1–10	46	(34)	21	(32)	
10.1–20	30	(22)	10	(15)	
>20	8	(6)	7	(11)	
Missing	0	(0)	1	(2)	
Prostate volume (cc)					0.05
≤26	60	(44)	17	(26)	
26.1–35	31	(23)	14	(21)	
35.1–50	18	(13)	15	(23)	
>50	6	(4)	7	(11)	
Missing	21	(15)	13	(20)	
Clinical stage					0.29
T1	38	(28)	26	(39)	
T2	86	(63)	37	(56)	
T3	2	(1)	0	(0)	
Missing	10	(7)	3	(5)	
Gleason score					0.42
4+3	34	(25)	20	(30)	
8–10	102	(75)	46	(70)	
Gleason secondary pattern					0.49
Grade 3	35	(26)	20	(30)	
Grade 4/5	101	(74)	46	(70)	
Downgrade at prostatectomy					<0.01*
No	80	(59)	54	(82)	
Yes	56	(41)	12	(18)	

* Statistically significant $P < 0.05$.

Other factors, including year of diagnosis, clinical stage, and number of biopsy cores, had no bearing on likelihood of downgrading.

Several multivariable analyses were undertaken to evaluate factors associated with downgrading. The model shown in Table 2 identifies several important clinical factors. The presence of mixed high and low grade cores (OR 3.0, 95% CI 1.3–7.1, $P < 0.01$) and Gleason 4+3 vs. 8–10 (OR 2.4, 95% CI 1.1–5.4, $P = 0.03$) was statistically associated with downgrading. In contrast, increasing PSA at diagnosis was not associated with downgrading (OR 1.0, 95% CI 0.9–1.0, $P = 0.11$). The model shown in Table 3 includes detailed biopsy information. Despite the fact that percent of positive cores with high grade and proportion of positive tissue containing high grade cancer were highly correlated (r = 0.88), we felt that inclusion of both of these variables was warranted. The proportion of positive cores containing high grade cancer (per 10% increment) was independently associated with lower odds of downgrading (OR 0.7, 95% CI 0.6–0.9, $P < 0.01$). The percent of total tissue containing prostate cancer (per 10% increment) showed a trend toward lower odds of downgrading (OR 0.8, 95% CI 0.6–1.0, $P = 0.05$).

Finally, a full model that included clinical and detailed biopsy characteristics was created and is presented in Table 4. The proportion of positive cores containing high grade cancer (per 10% increment) was significantly associated with downgrading (OR 0.8, 95% CI 0.7–0.9, $P < 0.01$). Similarly, the percent of total tissue containing prostate cancer (per 10% increment) was significantly associated with downgrading (OR 0.7, 95% CI 0.6–0.9, $P = 0.01$).

4. Discussion

Multiple studies have drawn attention to the problem of under-sampling of prostate cancer by ultrasound-guided biopsies, even in the era of extended-template mapped biopsies. Most of these have focused on under-grading and/or under-staging of apparently low-risk tumors [17–19]. While under-grading and under-staging could lead to under-treatment of higher-risk prostate cancer, in fact these problems tend to drive over-treatment, since awareness of under-sampling increases patient and clinician anxiety and thereby impedes acceptance and maintenance of active surveillance regimens [20–22]. However, under-sampling can also lead to over-grading, particularly if the overall biopsy is graded based on the highest grade biopsy core. Over-grading puts patients at risk for over-treatment. This study intended to quantify incidence and predictors of over-grading by examining those cases which were downgraded between biopsy and prostatectomy.

Age and clinical factors such as PSA, clinical stage, and prostate volume did not influence downgrading at prostatectomy. Rather, downgrading can be predicted by detailed, but commonly measured, information from the biopsy cores. In particular, and perhaps not surprisingly, a lower percent of positive cores with high grade disease and a lower percent of total tissue involved with prostate cancer were both significantly associated with downgrading.

Our findings are consistent with results from the study by Yang et al.; however, that study was limited to patients who only had cores containing high grade disease [14]. The current study showed similar results, but included patients with both high and low grade cores. In addition, a study by Rubin et al. demonstrated that tumor area containing high grade disease on biopsy was predictive of the percent of

Table 2
Detailed biopsy information in subjects with mixed and homogenous Gleason scores on diagnostic prostate biopsy

Characteristic	Low and high grade primary (n = 136)		Only high grade primary (n = 66)		
	Median	(Range)	Median	(Range)	P value
Biopsy cores taken	13	(10–62)	12	(10–46)	0.8
Biopsy cores % positive	42	(8–100)	29	(3–100)	0.02*
% positive cores w/HG	50	(8–93)	100	(80–100)	<0.01*
Total length taken (mm)	91	(16–305)	61	(8–214)	<0.01*
Total length % positive	26	(4–82)	25	(5–80)	0.28
% Positive total length w/HG	59	(1–100)	100	(100–100)	<0.01*

* Statistically significant $P < 0.05$.

high grade disease at prostatectomy, but their results were obtained using NIH image program, which is not routinely available [12]. The practicality of determining volume using sophisticated imaging may be prohibitive outside academic medical centers. In contrast, the Gleason score of each biopsy specimen is regularly measured in clinical practice and, therefore, the proportion of cores positive with high grade cancer could be a useful tool, and substantially more straightforward to determine.

The current study demonstrated that as the length of total tissue containing cancer increases, downgrading becomes less common. These results are consistent again with findings by Yang et al. who demonstrated a relationship of microfoci of high grade disease and downgrading at surgery [14]. However, again we expanded the results of this finding to patients with a greater percent of tumor present at biopsy. It is interesting that the percent of tissue containing high grade cancer dropped out of the stepwise model. This suggests that the combination of proportion of cores positive with high grade disease and total tissue containing cancer are more strongly associated with downgrading in our cohort than the percent of tissue containing high grade disease alone.

This study raises the awareness of the risk of over-grading in patients who have minimal disease on biopsy, or a majority of low grade cores on biopsy. Minimizing over-treatment is critical in order to limit the impact of over-detection, which results from intensive PSA screening [23]. Recognition of patients who may be over-graded could help to select those with low PSA and early stage that could be candidates for active surveillance. An initial report of such patients, most of whom underwent a repeat biopsy to confirm grade and volume of disease, suggests similar results compared with the very low risk patients which comprise most series [24]. In addition, as most patients present with low PSA and low stage disease, grade is often the primary determinant of need for lymphadenectomy in contemporary patients. As the yield of positive nodes at lymphadenectomy continues to decline, the concept of over-grading adds to the argument that the risk/benefit ratio and cost effectiveness of lymphadenectomy continues to decline [25]. Finally, radiation protocols often include risk-adapted strategies for the use of whole pelvis radiation, prostate boost, and androgen deprivation [26]. Understanding which patients may be over-graded could decrease the need for each.

The main potential limitation of this study is that biopsy and prostatectomy specimens were reviewed by different pathologists (although centralized review of outside biopsies was performed as has been recommended) [27]. However, because roughly two-thirds of the biopsies were performed by referring physicians, these slides were not available for re-review for this study. We believe that only

Table 3
Multivariate analysis of clinical predictors of downgrading at prostatectomy

Covariate	OR	(95% CI)	P value
Age at diagnosis (per 1 year increase)[a]	1.04	(0.98–1.10)	0.21
Year of diagnosis (per 1 year increase)[a]	1.04	(0.91–1.20)	0.56
Diagnostic biopsy at UCSF (no vs. yes)	1.11	(0.50–2.44)	0.80
PSA at diagnosis (per 1 ng/ml increase)[a]	0.95	(0.89–1.01)	0.12
Clinical T stage (T1 vs. T2/T3)	0.93	(0.73–1.20)	0.59
Prostate volume (per 1 cc increase)[a]	1.00	(0.97–1.03)	0.9
Gleason primary (mixed vs. all HG)	3.06	(1.30–7.18)	0.01*
Gleason secondary (3 vs. 4/5)	2.68	(1.20–6.01)	0.02*

[a] Continuous variable.
* Statistically significant $P < 0.05$.

Table 4
Multivariate analysis of detailed biopsy predictors of downgrading at prostatectomy

Covariate	OR	(95% CI)	P value
Biopsy cores taken (per 1 core increase)[a]	0.99	(0.94–1.05)	0.81
Biopsy cores % positive (per 1% increase)[a]	0.99	(0.97–1.01)	0.34
% Positive cores w/HG (per 1% increase)[a]	0.97	(0.95–0.99)	<0.01*
Total length taken (per 1 mm increase)[a]	1.00	(0.99–1.01)	0.77
Total length % positive (per 1 % increase)[a]	0.98	(0.95–1.00)	0.05
% Positive total length w/HG (per 1% increase)[a]	1.00	(0.98–1.03)	0.74

[a] Continuous variable.
* Statistically significant $P < 0.05$.

re-reviewing some slides is more likely to introduce systematic bias into the results than is interobserver variability. Furthermore, amongst urologic pathologists, Gleason grade agreement is substantial ($\kappa = 0.68$) [28]. In addition, while the overall incidence of downgrading between biopsy and prostatectomy might change if the same individual reads both, we believe that the sampling error in biopsy itself is the main cause of our findings. Finally, it seems even less likely that interobserver variability could confound the association that we present between downgrading and two significant predictors—the percent of cores positive with high grade and the percent of total tissue with cancer.

Other limitations include that generalization to patients undergoing radiation may be limited since radiation patients were not included in the current study. Furthermore, there is some evidence that patients who are downgraded at radical prostatectomy have risk of biochemical recurrence, which is between those who were not downgraded and those who had lower grade disease on biopsy [29]. Although Gleason pattern 4 or 5 was present as a tertiary grade in 13% of patients, this is a minority of the 34% of the cohort who were downgraded. This suggests that some portion of downgrading is due to sampling of minute quantities of high grade disease (unrecognized on sections at prostatectomy) or as an artifact caused by tangential sections of prostate glands at biopsy or perhaps even processing of biopsy specimen. Finally, grade migration has occurred since the early 1990s. However, the vast majority involves a change in Gleason 2–5 to Gleason 6 [30]. In addition, 90% of the current cohort was diagnosed after 2000 and year of diagnosis was not associated with downgrading in the multivariable model. Therefore, it is unlikely that grade migration played a significant role in the current findings.

5. Conclusion

Downgrading following radical prostatectomy is a common event. Biopsy over-grading may preclude men from active surveillance or lead to unnecessary lymphadenectomy, excess radiation, or prolonged hormone therapy. The proportion of positive biopsy cores that are high grade and the percent of total tissue containing cancer should be incorporated into decision making.

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