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The association between prostate size and Gleason score upgrading depends on the number of biopsy cores obtained: results from the Shared Equal Access Regional Cancer Hospital Database

Ryan S. Turley¹, Martha K. Terris^{2,3}, Christopher J. Kane^{4,5}, William J. Aronson^{6,7}, Joseph C. Presti Jr^{8,9}, Christopher L. Amling¹⁰, Stephen J. Freedland^{1,11,12}, and the SEARCH Database Study Group

¹Division of Urological Surgery, Duke Prostate Center, Duke University School of Medicine, Durham, NC

²Urology Section, Veterans Affairs Medical Center, Medical College of Georgia, Augusta, GA

³Section of Urology, Medical College of Georgia, Augusta, GA

⁴Urology Section, Veterans Affairs Medical Center, University of California, San Francisco School of Medicine, San Francisco, CA

⁵Department of Urology, University of California, San Francisco School of Medicine, San Francisco, CA

⁶Urology Section, Veterans Affairs Greater Los Angeles Healthcare System, UCLA School of Medicine, Los Angeles, CA

⁷Department of Urology, UCLA School of Medicine, Los Angeles, CA

⁸Department of Urology, Stanford University School of Medicine, Veterans Affairs Medical Center, Palo Alto, CA

⁹Urology Section, Veterans Affairs Medical Center, Palo Alto, CA

¹⁰Division of Urology, University of Alabama, Birmingham, AL

¹¹Urology Section, Veterans Affairs Medical Center, Duke University School of Medicine, Durham, NC, USA

¹²Department of Pathology, Duke University School of Medicine, Durham, NC, USA

Abstract

OBJECTIVE—To test the hypothesis that the association between prostate size and risk of Gleason grade upgrading varies as a function of sampling.

PATIENTS AND METHODS—We examined the association between pathological prostate weight, prostate biopsy scheme and Gleason upgrading (Gleason ≥ 7 at radical prostatectomy, RP)

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Correspondence: Stephen J. Freedland, Division of Urologic Surgery and the Duke Prostate Center, and Departments of Surgery and Pathology, Box 2626, Duke University Medical Center, Durham, NC 27710, USA. steve.freedland@duke.edu.

CONFLICT OF INTEREST

None declared.

Study Type – Prognosis (retrospective cohort study)

Level of Evidence 2b

among 646 men with biopsy Gleason 2–6 disease treated with RP between 1995 and 2007 within the Shared Equal Access Regional Cancer Hospital Database using logistic regression. In all, 204 and 442 men had a sextant (six or seven cores) or extended-core biopsy (eight or more cores), respectively. Analyses were adjusted for centre, age, surgery, preoperative prostate-specific antigen level, clinical stage, body mass index, race, and percentage of cores positive for cancer.

RESULTS—In all, 281 men (44%) were upgraded; a smaller prostate was positively associated with the risk of upgrading in men who had an extended-core biopsy ($P < 0.001$), but not among men who had a sextant biopsy ($P = 0.22$). The interaction between biopsy scheme and prostate size was significant (P interaction = 0.01).

CONCLUSIONS—These data support the hypothesis that the risk of upgrading is a function of two opposing contributions: (i) a more aggressive phenotype in smaller prostates and thus increased risk of upgrading; and (ii) more thorough sampling in smaller prostates and thus decreased risk of upgrading. When sampled more thoroughly, the phenotype association dominates and smaller prostates are linked with an increased risk of upgrading. In less thoroughly sampled prostates, these opposing factors nullify, resulting in no association between prostate size and risk of upgrading. These findings help to explain previously published disparate results of the importance of prostate size as a predictor of Gleason upgrading.

Keywords

prostate cancer; prostate weight; upgrading; biopsy cores; risk

INTRODUCTION

At present, patients with prostate cancer are offered a wide range of treatment options, ranging from active surveillance to radical prostatectomy (RP) to various forms of ablative therapy (i.e. radiation therapy, cryotherapy, etc.). When making management decisions, clinicians often rely heavily on the biopsy Gleason score. For instance, certain treatments, including active surveillance and brachytherapy, might be best suited to patients with biopsy scores showing low-risk characteristics (i.e. Gleason sum ≤ 6). Furthermore, high-risk features on biopsy (i.e. Gleason sum 4 + 3 or greater) might warrant the addition of adjuvant therapy, including pelvic lymph node irradiation or androgen suppression for those undergoing radiotherapy. For these reasons, confidence in the biopsy score carries important clinical implications.

Unfortunately, discordance between the biopsy and true pathological Gleason score has been well documented. In fact, a previous study from the Shared Equal Access Regional Cancer Hospital (SEARCH) database found that biopsy and Gleason sums differed in 48% of all cases [1], in line with several other studies [2–5]. Given the high prevalence of upgrading, and the fact that true pathological Gleason sum can only be defined after RP, biopsy features and clinical variables predictive of Gleason sum upgrading become critical when choosing amongst various management options.

Previously, we found greater PSA levels, more biopsy cores with cancer and obesity to be positively associated with Gleason score grading [1]. Recently, we also reported that smaller prostate volumes, as determined by TRUS, were significantly more likely to be upgraded [6]. However, other studies examining the association between prostate size and upgrading have produced conflicting results [7–9]. When searching for an explanation for these disparate reports we found the number of prostate biopsy cores obtained varied amongst the different reports. Given that taking more biopsy cores better predicts the true underlying pathological Gleason score [10,11], we tested whether Gleason upgrading is interdependent on both prostate size and biopsy core number. Given that smaller prostates are more likely to

have high-grade disease and cause biochemical recurrence [12], we hypothesized that smaller prostates are more likely to have a more aggressive cancer inherently prone to be upgraded. Larger prostates, although less likely to harbour high-grade cancer, are more likely to be under-sampled during biopsy, simply because they are larger. Therefore, we predicted that the risk of upgrading in larger prostates should decrease as the number of biopsy cores increases. Thus the objective of the present study was to further define the relationship between prostate sampling (i.e. number of biopsy cores obtained) and prostate size in predicting clinically relevant Gleason score grading.

PATIENTS AND METHODS

With Institutional Review Board approval from each institution to abstract and combine data, we combined data from patients undergoing RP at the Veterans Affairs Medical Centers in West Los Angeles, CA, Palo Alto, CA, Augusta, GA, and Durham, NC into the SEARCH database [13]. Patients treated with preoperative androgen deprivation or radiotherapy were excluded. Given that a significant PSA-recurrence-free survival disadvantage for men with a biopsy Gleason score of ≥ 7 has been well documented [14,15], we focused on upgrading for men diagnosed with low-grade Gleason scores (i.e. 2–6) at biopsy. Also, these men have the most options available, including some not ideally suited to men with higher-grade disease (i.e. active surveillance), and thus it is within this group that Gleason score upgrading might have the greatest clinical impact. As our goal was to compare upgrading with standard sextant biopsy vs extended-core biopsy, of the 1064 men within SEARCH with a biopsy Gleason 2–6 tumour, we excluded those with fewer than six biopsy cores obtained (105) or those with missing biopsy core data (159). Similarly, men with missing data for pathological weight (83), pretreatment PSA level (three), percentage of cores with cancer (11), or clinical stage (21) were excluded. Men with missing data for body mass index (BMI, 36) were also excluded, as obesity is positively associated with upgrading [1]. This resulted in a final study population of 646 men.

Pathological specimens were sectioned as previously described [16]. The protocol for processing RP specimens was similar across sites with two of four using step-sectioning with 3–5 mm intervals and embedding all sections for analysis. The third centre used representative sections of the apex, base, inferior, mid and superior aspects of the gland, including any grossly evident tumour, and seminal vesicles as per the protocol outlined by experienced genitourinary pathologists [17]. At the fourth centre the distal periurethral plane was removed and sectioned perpendicular to the distal margins. The prostate was sectioned from distal to proximal margin, including seminal vesicles. The bladder neck was examined separately.

In our previous study [6], we found that small prostate volumes as determined by TRUS were more likely to be upgraded. However, given that only 313 of the 646 men meeting the study entry criteria had TRUS volumes available, we were unable to examine the interaction between prostate size as assessed by TRUS and prostate sampling. Therefore, in the present study we used pathological prostate weight as a surrogate for preoperative TRUS volume. Previous studies, including one from the SEARCH database, showed that pathological weight correlates accurately with TRUS-based volume measurements [18,19]. For the present study, prostate weight was analysed as both a log-transformed continuous variable and a categorical variable. To create weight categories with sufficient numbers to complete multiple subanalyses while using clinically relevant categorizations, the patients were grouped as ≤ 30 g (142 men), 31–50 g (322) and > 50 g (182). Patients were also categorized according to the number of biopsy cores obtained, i.e. six or seven cores (204) vs eight or more cores (442). Gleason score was examined as a categorical variable of 2–6 and ≥ 7 . As

the study population was limited to men with a biopsy Gleason 2–6 cancer, patients were classified as upgraded when the RP specimen Gleason grade was ≥ 7 .

The distribution of baseline clinical and demographic characteristics was compared between the biopsy core groups using a two-tailed *t*-test for continuous variables and chi-squared tests for categorical variables. In cases of non-normally distributed continuous variables, the rank-sum test was used. Odds ratios of upgrading relative to no upgrading (i.e. no change) for each prostate size group relative to the largest prostate size group (>50 g) were determined using logistic regression. Analyses were adjusted for potential confounding variables including PSA level (continuous, after logarithmic transformation), age (continuous), year of surgery (continuous), surgical centre (categorical, 1–4), percentage of biopsy cores containing tumour (continuous), clinical stage (T2/3 vs T1), race (black, not black-not white, vs white), and BMI (25.0–29.9, ≥ 30.0 vs <25.0 kg/m²). Potential interactions between the biopsy core category and prostate weight were tested by including the cross-product term, which was calculated as pathological weight (continuous, after logarithmic transformation) multiplied by the categorical biopsy core group variable (0 or 1), into the logistic regression model, and evaluating the coefficient with the Wald test. Finally, a locally weighted regression (LOWESS) analysis was used to plot the association between prostate size and risk of upgrading stratified by biopsy core group. The distribution of all clinical and pathological variables was similar among the SEARCH sites and thus data from all centres were combined for analyses.

RESULTS

There were significant differences in demographic and clinical characteristics between men who had sextant or extended-core biopsy schemes (Table 1). Those who had an extended-core biopsy were treated more recently ($P < 0.01$), had slightly lower PSA levels ($P = 0.04$), a lower percentage of biopsy cores with cancer ($P < 0.01$), and a larger prostate ($P < 0.01$). There were no significant differences between biopsy groups in terms of race ($P = 0.95$), age ($P = 0.11$), BMI ($P = 0.97$), or clinical stage ($P = 0.91$) (Table 1).

Similar to our previous study using TRUS volume [6], overall prostate weight was significantly related to upgrading, with smaller prostates being more likely to be upgraded on both crude and adjusted analysis ($P < 0.001$, Table 2). To address our hypothesis that the relationship between prostate size and upgrading was also dependent on the number of biopsy cores obtained, we examined whether smaller prostates would still be more likely to be upgraded when biopsied with six or seven cores vs eight or more. For men biopsied with six or seven cores there was no significant relationship between upgrading and prostate size, for either crude or multivariate analyses (Table 2). However, among men biopsied with eight or more cores, the unadjusted risk of upgrading decreased significantly as prostate weight increased ($P < 0.01$). This relationship became even more pronounced after adjusting for multiple clinical characteristics (Table 2). For example, men with a prostate of <30 g were more than five times as likely to be upgraded than men with prostates of >50 g (Table 2). Overall, the interaction between prostate weight and biopsy-core group for predicting the risk of upgrading was statistically significant (P interaction = 0.01).

Finally, to further describe Gleason upgrading as an interdependent function between prostate size and sampling, a LOWESS plot was generated to estimate the probability of upgrading for each biopsy core subgroup. In this model, the risk of upgrading in men with six or seven cores remained close to 50% regardless of prostate size, whereas the probability of upgrading for men who had eight or more cores became progressively smaller as prostate size increased (Fig. 1).

DISCUSSION

The management of men after RP is partly dictated by the final pathological Gleason score. Other treatments, particularly radiotherapy, brachytherapy and active surveillance, do not provide the luxury of a final pathological Gleason score. Thus, clinicians managing patients choosing one of these non-surgical therapies must rely on the biopsy-derived Gleason sum. Unfortunately, it is well-documented that the pathological Gleason score frequently differs from biopsy Gleason scores [2-5]; indeed, a previous study from our group found a discordance rate of 48% [1]. A worrisome clinical scenario is when a patient with underlying high-grade cancer is categorized as low-risk because his prostate needle biopsy undergraded his true histology.

In essence, upgrading can be considered a marker of accuracy for the biopsy Gleason score, i.e. lower rates of upgrading would indicate a higher accuracy of biopsy and strong correlation between the biopsy and pathological Gleason sum. Assuming equal rates of high-grade disease across all prostate sizes, and equal numbers of biopsy cores, larger glands would be expected to be stochastically more likely to be upgraded, as a smaller fraction of the prostate gland would be sampled. We previously showed, among men who had predominantly extended-core biopsies, that men with larger TRUS volumes were significantly less likely to be upgraded [6]. However, reports from other groups have produced conflicting results [7-9]. When analysing these previous studies the sampling, as defined by the number of prostate needle biopsies obtained, varied. For example, our previous study [6] was predominantly based on extended core biopsies, whereas other previous studies included primarily sextant core biopsies [7,9]. Given that we and others have already shown that extended core biopsies (defined as eight or more cores) were less likely to be upgraded [1,10,11], we hypothesized that upgrading not only depends on prostate size but also on the number of cores taken. More specifically, the number of biopsy cores obtained might modify the association between prostate size and upgrading.

Using a multicentre cohort of men treated with RP of whom most had extended core biopsy, we confirmed our earlier results, in that when all men were examined together, larger prostates were less likely to be upgraded. However, when stratified by the number of biopsy cores obtained, we found no significant association between Gleason upgrading and prostate size among men who had a sextant core biopsy (six or seven cores). However, when an extended core biopsy (i.e. eight or more cores) was used, larger prostates were significantly less likely to be upgraded. In a LOWESS model aimed at estimating the risk of upgrading as a function of both prostate size and biopsy category, we showed the same relationship (Fig. 1), i.e. the risk of upgrading for men biopsied with a sextant core scheme remained relatively constant across all prostate weights, whereas the risk of upgrading for men biopsied with eight or more cores steadily decreased as prostate weight increased. Notably, the risk of upgrading for men biopsied with six or seven cores remained consistently high (~50%) regardless of prostate size. Taken together, this study suggests that prostate size only predicts clinically significant upgrading in the setting of an extended core biopsy.

Based on these results, we propose that the risk of upgrading is interdependent on two opposing forces, i.e. prostate size and sampling. In terms of prostate size, we propose two possible explanations to account for the positive association between smaller prostates and Gleason upgrading in the extended-core biopsy group. One possibility might be that smaller glands are more likely to be upgraded because they inherently have a more aggressive phenotype. Small prostate size is linked to lower levels of androgens such as testosterone [20] and dihydrotestosterone [21,22], and lower levels of intraprostatic growth factors such as insulin and IGF-1 [23-25], all of which are involved in prostate cancer cell growth and differentiation. It has been hypothesized that lower levels of these hormones and growth

factors in small prostates either produce a hormonal milieu in which only aggressive cancers can grow, or perhaps even promote the growth of high-grade cancer [12]. Supporting this theory, we previously found that patients with prostate cancer with smaller prostates have more high-grade cancers, more advanced disease, and are more likely to have progression after RP [12]. Our previous report was recently confirmed by the study of Briganti *et al.* [26], which also showed that smaller prostates were associated with higher rates of high-grade tumours, extracapsular extension and seminal vesicle invasion. Finally, others have also shown that a smaller prostate is associated with more aggressive disease [27,28].

The second possibility to help explain the positive association between Gleason upgrading and smaller prostates might be that men with smaller prostates have higher PSA densities (PSAD). Increasing PSAD is associated with higher-grade disease [16,29], e.g. if two men are biopsied and have similar total PSA serum levels, the man with the smaller prostate will have a higher PSAD and will therefore be more likely to harbour high-grade cancer, and perhaps be more likely to be upgraded after surgery. Thus, a verification bias might account for smaller prostates being more likely to be upgraded, as most prostate biopsies are PSA-driven.

If smaller glands are more likely to be upgraded, then intuitively, larger glands should conversely be less likely to be upgraded, as they would either have a less aggressive phenotype or have a lower PSAD. Indeed, a recent study by Kousouf *et al.* [8], that only used extended-core biopsies, found that men with larger prostates were indeed less likely to be upgraded and more likely to have well-differentiated tumours. However, Kulkarni *et al.* [7] examined men who had undergone a classic sextant core biopsy, and found the opposite relationship, i.e. larger prostates were more likely to be upgraded. Thus, despite larger prostates being generally less likely to contain high-grade tumours, less thorough sampling (i.e. classic sextant-core biopsy) might leave enough high-grade tumours undetected such that the association between larger prostates and a decreased risk of upgrading is lost. The present study, which assessed both sampling and prostate size, potentially reconciles these conflicting reports by showing that a small prostate indeed predicts Gleason upgrading, but only in well-sampled prostates.

The finding that prostate size and biopsy core number together define an association for Gleason upgrading has significant clinical implications. In particular, men with larger prostates (i.e. >50 g) and Gleason score 2–6 cancer have a lower likelihood of being upgraded when obtaining an extended core biopsy. Therefore, providers for these patients can be more confident of their management decisions as they relate to Gleason score, especially if opting for treatments other than RP. Conversely, clinicians treating men with small prostates (i.e. <50 g) sampled with at least eight biopsy cores, might consider more aggressive approaches, including neoadjuvant/adjuvant therapies, or perhaps a more frequent follow-up after treatment. This is especially true if the patient also has other known risk factors for upgrading, e.g. greater PSA levels, more biopsy cores with cancer, or obesity [1]. For men initially diagnosed with a sextant-core biopsy, as prostate size was not associated with the risk of upgrading, clinicians should use other available information as described above to estimate the risk of upgrading.

The present study has some limitations: First, it includes pathological data from several centres accrued over a 12-year period, leading to variability in pathological examinations. However, for each patient, the time from biopsy to surgery was relatively short, with all biopsy and pathological specimens being read in the same centre with the same Gleason grading criteria. Also, the year of surgery was controlled in all multivariate analysis to minimize effects from the long study period. Second, due to the limited number of patients in our database having complete data for TRUS volumes, we used pathological weight as a

surrogate to draw conclusions from other studies using TRUS volume. Regardless, we define a clear interaction between prostate weight and biopsy core number. Furthermore, we previously reported that TRUS volume correlates well with pathological prostate weight [19]. In some subsets of data, the sample size was relatively small. However, the LOWESS analysis, which examined prostate weight as a continuous function with local weighting, showed that among men with an extended core biopsy, as prostate size increased, the risk of upgrading decreased. Thus, the results were not solely driven by the extremes of prostate weight, but appear to be clinically relevant across the whole spectrum of prostate sizes. Also, the retrospective nature of this study introduces the inherent biases associated with all retrospective work. Finally, we limited our study to men with biopsy Gleason 2–6 disease, as upgrading from this group might have the greatest impact on disease management. Future studies are needed to address the risk of upgrading for men with higher grade disease on biopsy.

In conclusion, in this study of men undergoing RP to treat prostate cancer, smaller prostates were more likely to be upgraded when obtaining an extended-core biopsy scheme, but not with a sextant core biopsy. Men with larger prostates biopsied with eight or more cores had the lowest rates of clinically significant upgrading. These data support the hypothesis that the risk of upgrading is influenced by both prostate size (a surrogate for either tumour phenotype or high PSAD) and number of biopsy cores obtained (a measure of the extent of sampling). In the presence of more thorough sampling (extended core), the phenotype/PSAD association is dominant and smaller prostate size is linked with an increased risk of upgrading. In less thoroughly sampled prostates (sextant core), these opposing factors appear to nullify each other, resulting in no overall association between prostate size and upgrading risk. For these patients, the overall risk of upgrading remained consistently high (~50%) across all prostate sizes. These findings might reconcile disparate published reports of prostate size and upgrading where varying numbers of biopsy cores were obtained.

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Abbreviations

RP	radical prostatectomy
BMI	body mass index
SEARCH	Shared Equal Access Regional Cancer Hospital
PSAD	PSA density
LOWESS	locally weighted regression

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FIG. 1. The LOWESS plot of the risk of upgrading as a function of prostate weight stratified by the number of biopsy cores obtained

TABLE 1
The demographic and clinical characteristics of men with Gleason 2–6 prostate cancer stratified by biopsy core group

Characteristic	No. of biopsy cores		P
	6–7	≥8	
Total, <i>n</i> (%)	204 (31)	442 (69)	
Race			
White	100 (49)	211 (48)	0.95*
Black	92 (45)	204 (46)	
Other	12 (6)	27 (6)	
Mean (SD) age, years	61.2 (6.9)	60.3 (6.4)	0.11†
Median (IQR) year	1999 (97–02)	2002 (99–04)	<0.01‡
BMI, kg/m ²			0.97*
<25	59 (29)	115 (27)	
25–29.9	88 (42)	189 (44)	
30–34.9	42 (21)	100 (22)	
≥35	15 (8)	38 (8)	
Median (IQR):			
PSA, ng/mL	6.7 (5.0–10.0)	6.2 (4.5–9.0)	0.04‡
% cores with cancer	33.3 (16.7–50.0)	20.0 (11.1–37.5)	<0.01‡
prostate weight, g	38.0 (28.0–48.5)	40.1 (32.0–55.0)	<0.01‡
Clinical stage, <i>n</i> (%)			
T1/2	125 (61)	288 (65)	0.91*
T3	79 (39)	154 (35)	

* chi-squared test

† two-tailed t-test

‡ rank-sum test; IQR, interquartile range (25–75%).

TABLE 2
The risk of Gleason upgrading as a function of prostate weight, stratified by biopsy core group

No. biopsy cores		Prostate weight (g)			P
		<30	30-50	>50	
All					
	Crude likelihood of upgrading, %	53.5	46.9	29.7	<0.01*
	Adjusted OR [‡] (95% CI)	3.87 (2.18–6.85)	3.14 (1.97–5.00)	R	<0.001 [‡]
6-7					
	Crude likelihood of upgrading, %	51.7	49.5	41.9	0.59*
	Adjusted OR [‡] (95% CI)	2.04 (0.77–5.40)	2.09 (0.87–5.03)	R	0.22 [‡]
≥8					
	Crude likelihood of upgrading, %	54.9	45.7	25.9	<0.01*
	Adjusted OR [‡] (95% CI)	5.72 (2.68–12.2)	3.89 (2.18–6.92)	R	<0.001 [‡]

* chi-squared test

[‡] P trend calculated by substituting logarithmic-transformed prostate weight into the logistic regression model.

[‡] Adjusted for age, race, BMI, pretreatment PSA level, clinical stage, percentage of cores involved with cancer, year of surgery, and surgical centre. R, referent category.