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Biopsy-Derived Gleason Artifact and Prostate Volume: Experience Using Ten Samples in Larger Prostates

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Prostate neoplasm · Gleason score · Biopsy · Prostate volume

Abstract
Purpose: To verify whether a significant relationship between the risk of Gleason upgrading and the prostate volume remains when the number of biopsies is increased for larger prostate volumes. ***Materials:*** A total of 281 biopsy-proven prostate adenocarcinoma cases who underwent radical prostatectomy (RRP) formed the cohort for this study. Change in transrectal ultrasound of the prostate (TRUS) biopsies number based on total gland volume was made simply by increasing the number of biopsies from 6 to 10 when prostate volume was >50 cc. The total number of cancers with Gleason pattern 4 or greater on biopsy and on RRP was tabulated over TRUS volume categories and tests for trend. ***Results:*** The proportion of Gleason score (GS) ≥7 at biopsy was 44.5% whereas, at RRP, it was 68.3%. The rate of upgrading from Gleason <7 at biopsy to GS ≥7 at RRP was 46.8%. No significant difference in terms of age, serum PSA, prostate volume and pT stage was found between not upgraded and upgraded cases ($p > 0.05$). As prostate volume categories increase, the number of cancers upgraded at RRP slightly increases in particular from prostate volume 30–39 to 40–49 cc (where only 6 biopsies were performed). However, either at biopsy or at RRP, the percentage of GS ≥7 tumors does not show a significant trend in changing ($p > 0.05$). ***Conclusions:*** We verified that the relationship between the risk of Gleason upgrading and prostate volume does not become significant simply by increasing the number of laterally directed biopsies from 6 to 10.

Introduction

Gleason grade from prostate biopsy specimens is important in guiding therapeutic decision-making in patients with prostate cancer. It has long been recognized that discordance exists between biopsy grade and true histological grade obtained at radical prostatectomy (RRP). From the literature it has been shown that 33–63% of the biopsy Gleason score (GS) are upgraded at RRP [1–4]. From an outcome research point of view, it is important to recognize that a prognostic stratification of patients by GS may prove correct in patients undergoing RRP, but not in patients where only the biopsy GS is available. The risk is that, using only the biopsy GS, some patients considered to be in the lower risk prognostic group might be in reality in the high-risk prognostic group [1].

Given that prostate cancer detection is negatively correlated with prostate volume [5–8], it is not inconceivable that the rate of upgrading at RRP may be non-uniform based on the size of the prostate [1]. The analyses on the

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Prostate Cancer Prevention Trial (PCPT) [9] strongly underlined that the higher number of high-grade tumors (Gleason pattern 4 or greater) in the finasteride group relates to a biopsy-derived artifact secondary to variations in gland volume. Recent data from Kulkarni et al. [1] revealed an inverse association between prostate volume and Gleason grade (4 or greater) at biopsy. Based on this finding the authors [1] hypothesized that an inability to detect such a volume-grade relationship with prostatectomy specimens from the same patients, based on differential tumor upgrading, would provide evidence of a biopsy-derived grading artifact in larger prostates. Either in the PCPT [9] or in the study of Kulkarni et al. [1], systematic sextant biopsies were performed for each patient, irrespective of the prostate volume revealed at transrectal ultrasound of the prostate (TRUS).

The aim of our study is to verify whether a significant positive relationship between the risk of Gleason upgrading and the prostate volume remains when the number of laterally directed biopsies is increased for larger prostate volumes. As in the PCPT [9] and in the study of Kulkarni et al. [1], we specifically analyzed upgrading from GS 6 (pattern 3 or less) to GS 7 (pattern 4 or greater). In particular, in a population of biopsy-diagnosed clinically localized prostate adenocarcinomas submitted to RRP, we analyzed: (1) the rate of upgrading from a Gleason pattern 3 or less to a Gleason pattern 4 or greater, from biopsy to RRP; (2) correlations between the biopsy or the RRP GS and other covariates; (3) comparison of upgraded and not upgraded cases regarding prostate volume, PSA, age and pathological T stage, and (4) the nature and the odds ratio of the upgrading according to prostate volume categories.

Materials and Methods

This is a single-center retrospective study. We analyzed all cases with a diagnosis of prostate adenocarcinoma obtained at a TRUS-guided biopsy, who underwent RRP at our institution from January 1999 to January 2006. No selection on the basis of PSA preoperative levels or prostate volume was performed. A total of 281 clinically localized, biopsy-proven prostate adenocarcinoma cases who underwent RRP, formed the cohort for this study. None of the patients had received preoperative hormonal therapies, including 5α-reductase inhibitors.

Indications for biopsy were an abnormal age-specific PSA (40–49 years: >2.5 ng/ml; 50–59 years: >3.5 ng/ml; 60–69 years >4.5 ng/ml; 70–79 years >5.5 ng/ml) and/or an abnormal digital rectal examination (DRE). All TRUS biopsies were performed using a uniform technique. TRUS and biopsy were performed using an end-fire ultrasound transducer and biopsy gun with an 18-gauge needle (Esaote Technos MP with a C10–5 transducer). Prostatic volumes were assessed using the prolate ellipsoid method. However, as common practice in our institution and as proposed in previous studies [10, 11], change in biopsies number based on total gland volume was made simply by increasing the number of biopsies from 6 to 10 when prostate volume was ≥50 cc. In particular, systematic, laterally directed sextant biopsies were performed for each patient with a total prostate volume <50 cc. For all prostate volumes ≥50 cc, we performed a laterally directed 10 biopsies (2 lateral peripheral zone biopsies of the base and 2 lateral peripheral biopsies of the mid-gland in addition to routine sextant biopsies). No other change in the number of biopsies based on prostate volume was made in our population. Hypoechoic lesions were sampled but were not submitted separately for pathological review.

All patients were submitted to RRP. Prostatectomy specimens were all evaluated at our institution by the same pathology group responsible for interpreting the initial biopsy results, according to a routine technique.

Covariates recorded for each patient included age, pre-biopsy PSA, TRUS volume, pathological T stage (pT) and GS at biopsy and RRP. After surgery a pathological staging was assigned according to the 1997 modification of the TNM classification. Tumor grade, either at biopsy or at RRP, was described according to the Gleason grading system. To be comparable with previous studies on the same topic [1], on the basis of the histological grade, patients were divided into two different groups: GS <7 (no Gleason pattern 4) and GS ≥7 (pattern 4 or greater).

Statistical Analysis

Statistical analyses were performed using SigmaStat and SigmaPlot 9.0 statistical software. Descriptive statistics were used to characterize the age of patients as well PSA, prostate volume, pathological T stage and the GS either at biopsy or at RRP.

In all analyses, on the basis of the biopsy and RRP GSs, cases were classified in GS <7 (no pattern 4) and GS ≥7 (pattern 4 or greater). Spearman correlation coefficients were calculated to measure the association among GS and the other covariates. Variations in the covariates in each GS group were reported using Mann-Whitney test. Simple variable logistic regression using each of the collected covariates was performed to ascertain risk factors for Gleason pattern 4 or greater on biopsy and RRP specimens. Gleason pattern 4 or greater was then regressed with the same covariates in multivariate analysis on biopsy and RRP specimens.

On the basis of the pathological T stage, patients were divided in pT2 and pT3 cases. No pT4 cases were found.

PSA and prostate volume were used either as continuous variables or categorized in: PSA <4.0, 4.1–10, and >10 ng/ml. Prostate volume 30–39, 40–49, 50–59, 60–69, and ≥70 cc. Prostate volume variable was tested for trend in all regressions. Odds ratios (OR) for each prostate volume category were also calculated to visualize the consistency of the trends. The total number of cancers with Gleason pattern 4 or greater on biopsy and RRP were tabulated over TRUS volume categories and tests for trend using the Cochran-Armitage test. Multiple logistic regression was used to determine which variable independently predicted Gleason pattern 4 or greater on biopsy and RRP. A two-tailed $p < 0.05$ was considered significant for all analyses.

Table 1. Demographic characteristics of the cohort

Cases	281
Age, years	65.27 ± 5.25 (66.0) range 50–74
PSA, ng/ml	12.58 ± 4.93 (12.0) range 1.30–24.80
Prostate volume, cc	64.53 ± 16.0 (63.0) range 30–100
pT2	137 (48.75%)
pT3	144 (51.25%)
Biopsy GS	
<7	156 (55.5%)
≥7	125 (44.5%)
RRP GS	
<7	89 (31.7%)
≥7	192 (68.3%)

Values are reported as number of cases, mean ± SD (median); range.

Table 2. Frequency of GS <7 (no pattern 4) and GS ≥7 (pattern 4 or greater) at biopsy and RRP (number of cases)

	Radical prostatectomy		
	<7	≥7	total
Biopsy			
<7	83	73	156
≥7	6	119	125
Total	89	192	281

Table 3. Association between the different covariates and GS at biopsy or at RRP (Spearman correlation coefficients (r) and p values are presented)

	GS at biopsy		GS at RRP	
	r	p	r	p
Age	0.015	0.867	0.037	0.730
Prostate volume	0.047	0.595	0.097	0.364
PSA	0.116	0.042	0.129	0.035
pT stage	0.148	0.012	0.153	0.009

Results

A total of 281 untreated clinically localized prostate adenocarcinoma patients who underwent RRP at our institution represents the population of our study. Table 1 shows the baseline demographics of this patient cohort. In particular the median age was 66.0 years, the median PSA serum level was 12.0 ng/ml and the median TRUS volume of the group was 63 cc.

Table 2 illustrates the frequency of GSs based on biopsy and RRP specimens from the same patient. The proportion of GS ≥ 7 (Gleason pattern 4 or greater) at biopsy was 44.5% (125/281 cases). Substantial upgrading occurred at RRP with a 68.3% (192/281 cases) rate of high-grade tumors. The rate of upgrading (46.8%) from Gleason <7 (no pattern 4) at biopsy to GS ≥7 (pattern 4 or greater) at RRP was much higher than the observed downgrading rate (4.8%).

Table 3 shows at the univariate analysis the Spearman correlation coefficients between the different covariates and the GS at biopsy or at RRP. Only pT stage and PSA but not the other covariates analyzed were significantly associated either with biopsy or RRP GS. Moreover, no significant differences in associations were found between biopsy and RRP GS.

Table 4 analyses differences in the covariates between patients who were and were not upgraded between biopsy and RRP GS. No significant differences in terms of age, serum PSA, prostate volume and pT stage were found between not upgraded and upgraded cases.

Table 5 illustrates the nature of the upgrading from biopsy to RRP according to prostate volume categories. As prostate volume categories increase, the number of cancers upgraded at RRP slightly increases, in particular from prostate volume 30–39 to 40–49 cc (where the number of biopsies remained 6). However, either at biopsy or at RRP, the percentage of GS ≥7 (pattern 4 or greater) tumors does not show a significant trend in changing (test for trend $p > 0.05$).

Similarly, using the lowest category (prostate volume 30–39 cc) as reference, the OR for a GS ≥7 does not significantly ($p > 0.05$) change according to prostate volume, either at biopsy or at RRP (table 6).

On the multivariate analysis, using a GS ≥7 at biopsy and at RRP as dependent variable (table 7), serum PSA and pT stage but not prostate volume were found to be significant independent predictors of a GS ≥7. Moreover, either for PSA or pT stage, no difference between biopsy and RRP GS was found.

Discussion

The analyses on the PCPT [9] underlined that the higher number of high-grade tumors in the finasteride group relates to a biopsy-derived artifact secondary to variations in gland volume. In the PCPT all prostate can-

Table 4. Differences in the covariates classifying the population in not upgraded and upgraded cases (Mann-Whitney test)

	Not upgraded cases: Biopsy GS <7 and RRP GS <7	Upgraded cases: Biopsy GS <7 and RRP GS ≥7	p value
Cases	83	73	
Age, years	65.69 ± 5.12 (66.0), range 50–74	65.36 ± 5.16 (66.0), range 50–74	0.229
PSA, ng/ml	12.38 ± 4.77 (12.0), range 1.3–23.0	12.61 ± 4.94 (12.06), range 1.4–24.80	0.270
pT2	42 (50.6%)	33 (45.2%)	0.456
pT3	41 (49.4%)	40 (54.8%)	
Prostate volume, cc	64.39 ± 15.89 (63.0), range (30–100)	64.23 ± 16.08 (63.0), range 30–94	0.442

Table 5. GS ≥7 (pattern 4 or greater) and changes between biopsy and RRP, over prostate volume categories

Volume, cc	Biopsies	GS ≥7, % (n/total)		Change (number of cases)
		biopsy	RRP	
30–39	6	50 (8/16)	75 (12/16)	4
40–49	6	38 (16/42)	67 (28/42)	12
50–59	10	46 (27/59)	68 (40/59)	13
60–69	10	44 (26/59)	73 (43/59)	17
≥70	10	46 (48/105)	66 (69/105)	21
p value for trend		0.652	0.368	–

Table 6. Odds ratio (OR) for a GS ≥7 (pattern 4 or greater) according to prostate volume categories (OR and 95% confidential interval (CI) using the lowest category (30–39 cc) as reference)

Prostate volume	GS ≥7 at biopsy		GS ≥7 at RRP	
	OR (95% CI)	p value	OR (95% CI)	p value
30–39 cc	1.0		1.0	
40–49 cc	0.61 (0.19–1.96)	0.552	0.66 (0.18–2.45)	0.752
50–59 cc	0.84 (0.27–2.55)	0.784	0.70 (0.20–2.47)	0.762
60–69 cc	0.79 (0.26–2.38)	0.779	0.85 (0.25–3.19)	0.880
≥70 cc	0.84 (0.29–2.41)	0.792	0.64 (0.19–2.12)	0.575

cers were diagnosed using sextant biopsies, irrespective of the prostate volume. Recently, Kulkarni et al. [1] reported a significant inverse relationship between prostate gland size and Gleason grade at biopsy. Also in this study, sextant biopsies were used in all patients irrespective of the prostate volume. Based on this finding, the authors [1] concluded that an inability to detect such a volume-grade relationship with RRP specimens from the same patient, based on differential tumor upgrading, would provide evidence of a biopsy-derived grading artifact in larger prostates.

To our knowledge, we first showed in the present study that the relationship between the risk of Gleason upgrading and prostate volume does not become significant simply by increasing the number of laterally directed biopsies from 6 to 10 in cases of prostate volumes ≥50 cc.

In our population, remaining in the range (33–61%) described in the literature [1–3], a 46.8% rate of upgrading from GS <7 (no pattern 4) at biopsy to GS ≥7 (pattern 4 or greater) at RRP was present. The heterogeneous, multifocal nature of prostate cancer is likely responsible for upgrading from biopsy to prostatectomy specimens.

Table 7. Multivariate analysis for prediction of GS ≥7 at biopsy and RRP (coefficient, 95% confidential interval (CI) and p values are presented)

Variable	Coefficient	95% CI	p value
At biopsy			
Age	0.09843	–0.0345–0.2190	0.1542
Prostate volume	0.09630	–0.0356–0.2285	0.1350
PSA	0.02860	0.0085–0.0413	0.0025
pT stage	0.00583	0.0032–0.0095	0.0006
At radical prostatectomy			
Age	0.08856	–0.0450–0.2286	0.1230
Prostate volume	0.09430	–0.0335–0.2256	0.1460
PSA	0.02430	0.0075–0.0410	0.0020
pT stage	0.00465	0.0026–0.0086	0.0003

Given that sextant prostatic systemic biopsies sample only about 90 mm of prostate tissue (6 × 15 mm cores), increased prostatic volume may significantly reduce the chance of detecting cancer [12]. The wide variation in gland size and shapes indicates that in smaller glands the

prostate biopsy leads to a more extensive sampling and less extensive or suboptimal sampling in larger prostates. Several groups have proposed new biopsy strategies, which often increase the number of biopsies and the section to be sampled or they perform biopsies more laterally. However, the question of optimal biopsy sites and number of cores is still unanswered. Djavan [12] proposed a nomogram that concerns the number of cores for biopsy required as a function of prostate size and patient's age. Chang et al. [10] proposed that combining systematic sextant and lateral peripheral zone biopsies would detect more prostate cancers. Similarly, Presti et al. [11] performed lateral peripheral zone biopsies of the base and mid-gland in addition to routine sextant biopsies. However, none of these studies specifically target the relationship between the number of biopsy cores and prostate volume in terms of risk of upgrading at the GS. As common clinical practice and as also proposed by other authors [10, 11], in the population examined in our study, patients with larger prostates (≥50 cc) were submitted to 2 lateral peripheral zone biopsies of the base and 2 of the mid-gland, in addition to routine sextant biopsies. In our population the risk of upgrading did not significantly increase according to the prostate volume and no significant difference in mean and median prostate volumes between no upgraded and upgraded cases was found.

Always using a sextant biopsy irrespective of the prostate volume, any Gleason pattern 4 or greater would have a higher chance of being sampled in small glands and the chance of sampling a section of high-grade cancer in larger glands is thus reduced. As has also been proposed by other authors [10, 11], by simply increasing the number of laterally directed biopsies to 10 when prostate volume is ≥50 cc, without further modifications for larger prostates, it appears that any Gleason pattern 4 or greater would have a similar chance of being sampled irrespective of the prostate volume, and finally the chance of sampling a section of high-grade cancer in larger glands would not be reduced. As shown in tables 6 and 7, modulating the number of biopsies from 6 to 10, prostate volume was not a significant predictor of high-grade disease, either at biopsy or at RRP and the percentage of GS ≥7 tumors detected at biopsy did not show a significant trend in changing according to the prostate volume. Unfortunately, we had no opportunity to calculate the ratio between the volume of prostate tissue sampled at biopsy and the total volume of the gland for each category.

Some differences between our study and that of Kulkarni et al. [1] should be recognized. The number of cases analyzed in our study is similar to that in the study of Kulkarni et al. [1], but our population showed a higher median serum PSA level (12.0 ng/ml in our study and 5.8 ng/ml in the study of Kulkarni et al.) and prostate volume (63.0 cc in our study and 40.8 cc in the study of Kulkarni et al.). The higher PSA and prostate volume reported in our population can be both explained by the fact that Kulkarni et al. [1] selected only cases with a PSA level <10 ng/ml, whereas in our study, no selection on the basis of PSA was done. Without any selection in the identification of the population, the real relationship between prostate volume and GS at biopsy could be better analyzed. Moreover, the higher median prostate volume described in our population more significantly sustains the evidence that a simple variation from 6 to 10 biopsies is able to exclude the effect of prostate volume on the risk of Gleason upgrading.

A second difference between the two studies must be evidenced. Kulkarni et al. [1] decided to classify TRUS volumes in quartiles. Similarly to other studies [5], we preferred to classify TRUS volumes in 10-cc gland-volume intervals, obtaining 5 different groups. In our opinion this is a more clinically useful classification, so that the results obtained can be more easily applied in clinical practice.

As expected, in our population, serum PSA and pT stage were the two variables found to be significant independent predictors of a GS ≥7, either at the univariate or at the multivariate analysis. Again, no difference was found between biopsy and RRP results and, in fact, no significant difference in PSA levels or pT stage distribution was found between no upgraded and upgraded cases. Several studies showed a significant relationship between GS and pT stage [13–15]. The analysis on PCPT data [9] underlined that serum PSA is a better marker for high-grade diseases.

Our study, together with that of Kulkarni et al. [1], can have broad urological consequences. On the basis of a persistent significant rate of upgrading a high GS at RRP, a prognostic stratification and a treatment choice on the basis of biopsy GS may prove not correct. Using systematic sextant biopsies irrespective of the prostate volume, this risk could be predicted to be higher in larger prostate volume and conversely, men with small prostates can be more assured that their biopsy GS represents the true histological grade. On the contrary, modulating the number of biopsies on the basis of prostate volume, TRUS volume cannot be used to predict the risk of high-grade Gleason upgrading at RRP.

Conclusions

In our experience, we first verified that the relationship between the risk of Gleason upgrading and prostate volume does not become significant by simply increasing the number of laterally directed biopsies from 6 to 10. In this way, any Gleason pattern 4 or greater would have a similar chance of being sampled irrespective of prostate volume. Further investigations on the effect of different changes in the number of biopsies and the risk of upgrading are needed.

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