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Upgrading and Downgrading of Prostate Cancer from Biopsy to Radical Prostatectomy: Incidence and Predictive Factors Using the Modified Gleason Grading System and Factoring in Tertiary Grades

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Abstract

Background—Prior studies assessing the correlation of Gleason score (GS) at needle biopsy and corresponding radical prostatectomy (RP) predated the use of the modified Gleason scoring system and did not factor in tertiary grade patterns.

Objective—To assess the relation of biopsy and RP grade in the largest study to date.

Design, setting, and participants—A total of 7643 totally embedded RP and corresponding needle biopsies (2004–2010) were analyzed according to the updated Gleason system.

Interventions—All patients underwent prostate biopsy prior to RP.

Measurements—The relation of upgrading or downgrading to patient and cancer characteristics was compared using the chi-square test, Student *t* test, and multivariable logistic regression.

Results and limitations—A total of 36.3% of cases were upgraded from a needle biopsy GS 5–6 to a higher grade at RP (11.2% with GS 6 plus tertiary). Half of the cases had matching GS 3 + 4 = 7 at biopsy and RP with an approximately equal number of cases downgraded and upgraded

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at RP. With biopsy GS 4 + 3 = 7, RP GS was almost equally 3 + 4 = 7 and 4 + 3 = 7. Biopsy GS 8 led to an almost equal distribution between RP GS 4 + 3 = 7, 8, and 9–10. A total of 58% of the cases had matching GS 9–10 at biopsy and RP. In multivariable analysis, increasing age ($p < 0.0001$), increasing serum prostate-specific antigen level ($p < 0.0001$), decreasing RP weight ($p < 0.0001$), and increasing maximum percentage cancer/core ($p < 0.0001$) predicted the upgrade from biopsy GS 5–6 to higher at RP. Despite factoring in multiple variables including the number of positive cores and the maximum percentage of cancer per core, the concordance indexes were not sufficiently high to justify the use of nomograms for predicting upgrading and downgrading for the individual patient.

Conclusions—Almost 20% of RP cases have tertiary patterns. A needle biopsy can sample a tertiary higher Gleason pattern in the RP, which is then not recorded in the standard GS reporting, resulting in an apparent overgrading on the needle biopsy.

Keywords

Gleason grade; Needle biopsy; Radical prostatectomy

1. Introduction

Numerous studies have assessed the correlation of Gleason score (GS) at needle biopsy with that of the corresponding radical prostatectomy (RP) [1]. In 2004 one of the authors of the current article led a consensus on updating the Gleason grading system, published in 2005 [2]. From this update and subsequent modifications, the major changes are that cribriform, glomeruloid, and poorly formed glands are now considered Gleason pattern 4 as opposed to pattern 3 in the old system. The GS is now derived by adding the most common and highest Gleason pattern on biopsy, as opposed to the original GS that added the most common and second most common pattern. There was also consensus on the prognostic importance of tertiary grade patterns in RP specimens.

Biopsy grade has assumed greater importance in recent years with a relative increase in men undergoing therapy other than RP, such as radiation therapy or active surveillance where the only tissue sampled is on the needle biopsy. Not only is there a potential for undertreatment resulting from undergrading on needle biopsy, but overtreatment (ie, additional radiotherapy) remains a concern for men whose biopsies are overgraded. The issue of accounting for tertiary grade patterns is significant as can be seen in almost 20% of RP specimens [3]. The current evaluation of a large number of cases analyzing the relationship between needle biopsy and RP GS improves on prior works by (1) accounting for the updated Gleason system in both the needle biopsy and RP, (2) reporting RP higher tertiary grade patterns, (3) including only cases with extended needle biopsy sampling, and (4) including RPs that were examined histologically in their entirety.

2. Patients and methods

The Institutional Urology Prostate Cancer Database was searched for cases of RP specimens removed between January 1, 2002, and December 21, 2010. Institutional review board approval was received. Cases were included only if the corresponding needle biopsy had at

least a 10-core sampling. Cases with neoadjuvant therapy were excluded. Treatment with 5α-reductase inhibitors was not an exclusion criterion for the present analysis. A total of 7643 RPs and corresponding needle biopsies formed the basis of the current study. Table 1 details the patient characteristics.

All RP specimens were serially sliced and submitted in their entirety for histologic examination. Cases were not re-reviewed for the purposes of this study.

The overwhelming majority of the patients were operated on within 3 mo from biopsy, so potential grade progression between procedures was not an issue. Most biopsies were performed at outside institutions, yet per hospital policy all outside biopsy slides were reviewed and regraded at our institution prior to RP. The grading of both biopsies and RPs was done by a group of predominantly nongenitourinary pathologists, although they often consulted the in-house genitourinary pathologists on difficult cases. The overall biopsy GS was based on the core with the highest GS. In RP cases with multifocal disease, the overall GS was based on the nodule with the highest GS.

Upgrading and downgrading were defined as an increase or decrease, respectively, from one prognostic grade group to another. Prognostic GS groups were 5–6, 3 + 4 = 7, 4 + 3 = 7, 8, and 9–10. Intermediate RP GS categories were created by adding the designation “T” to each existing category when a higher tertiary pattern was present. GS 5–6 could have a tertiary pattern 4 or 5, whereas T refers to tertiary pattern 5 only for the remaining categories. A tertiary pattern of the same prognostic Gleason group were not considered an upgrade (ie, GS 5–6 to GS 5–6T was not considered an upgrade). Prior studies demonstrate that the presence of a tertiary pattern is associated with an intermediate worsening of prognosis. For example, GS 6T has a prognosis between GS 6 and GS 3 + 4 = 7) [3,4]. The relation of upgrading or downgrading to age, preoperative serum prostate-specific antigen (PSA) levels, number of positive cores, maximum percentage of cancer per core, and RP weight was compared using the Student *t* test. In a prior study of >3000 needle biopsy specimens analyzed at our institution, between 10 and 15 cores were sampled in 67.5% of the cases with the remaining cases evenly distributed between <10 and >15 cores with only one patient with a sextant biopsy. Given the relatively narrow range of number of cores sampled, we have found in our data virtually the same statistical results whether the number or fraction of positive cores is used [1,5]. Because we did not have information on the number of cores sampled for a large proportion of our cases, we could not address the relation of the number of cores sampled to predict upgrading and downgrading.

Pathology weight was reported both as a continuous and categorical value to demonstrate that the differences in upgrading were more pronounced in the highest weight. The chi-square test assessed the relationship between upgrading and downgrading relative to clinical stage. The relationship of the same variables to upgrading or downgrading in multivariable analysis was assessed by logistic regression, with manual backward removal of nonsignificant variables. The concordance index (c-index) was used as a measure of the models' ability to discriminate grade change at RP and was calculated using the final regression model for upgrading and downgrading. Logistic regression analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC, USA). In a minority of patients, not

all the data were available for each variable, accounting for minor variation in the numbers in the tables.

3. Results

3.1. Relation of needle biopsy to radical prostatectomy Gleason score

Table 2 details the corresponding RP GS for each of the five needle biopsy GS groups. Of note, 36.3% of cases were upgraded from a needle biopsy GS 5–6 to a higher grade at RP; nearly 20% of the cohort had a tertiary Gleason pattern, and if one ignored the tertiary patterns, 25.1% were upgraded. Approximately 50% of the cases had matching GS 3 + 4 = 7 at biopsy and RP with an approximately equal smaller number of cases downgraded or upgraded. When the biopsy was 4 + 3 = 7, there was an almost equal split between 3 + 4 = 7 and 4 + 3 = 7 at RP. A biopsy of GS 8 led to an almost equal distribution between RP GS 4 + 3 = 7, 8, and 9–10. A total of 58% of the cases had matching GS 9–10 at biopsy and RP.

3.2. Predictors of upgrading from biopsy to radical prostatectomy

Table 3 details the association between preoperative clinical and pathologic variables and GS upgrading from a biopsy GS 5–6 to higher at RP. Of note, upgraded patients were older, had a higher PSA, more positive cores, a greater maximum percentage involvement of a given core, had smaller prostates, and more often an advanced clinical stage. In multivariable logistic regression analyses, increasing age ($p < 0.0001$), increasing preoperative serum PSA level ($p < 0.0001$), increasing maximum percentage of cancer per core ($p < 0.0001$), and decreasing RP weight ($p < 0.0001$) predicted upgrade from biopsy GS 5–6 to higher GS at RP; c-index = 0.685 (Table 4).

3.3. Predictors of downgrading from biopsy to radical prostatectomy

Correlations with preoperative parameters and downgrading from GS 3 + 4 = 7 to GS 5–6 are shown in Table 5. Of note, downgraded patients had a lower PSA, fewer positive cores, less maximum percentage involvement of a given core, larger prostates, and were clinical stage T1c or T2a.

Statistically significant predictors of downgrading from biopsy 3+4=7 to RP GS 5–6 were lower serum PSA ($p = 0.031$), lower maximum percentage of cancer per core ($p = 0.002$), and higher RP weight ($p = 0.019$); c-index = 0.629 (Table 4). Downgrading from any biopsy GS to a lower GS at RP included only lower serum PSA and lower maximum percentage of cancer per core as significant predictors (model not shown).

4. Discussion

The needle biopsy and corresponding RP GS may not be the same for several reasons: pathology error, borderline grades, and sampling error. Some of the more common pathology errors in grading limited needle biopsy specimens include (1) overcalling Gleason pattern 4 on tangentially sectioned small glands of pattern 3 that mimic poorly formed glands, (2) undercalling cribriform Gleason pattern 4 as pattern 3, and (3) undercalling GS 9–10. Because the differences between different Gleason patterns are a continuum, there are borderline grades between small glands of pattern 3 and poorly formed glands of pattern 4.

Similarly, there are borderline grades between poorly formed glands of pattern 4 and pattern 5 with barely appreciable glandular differentiation. The most common sampling error occurs when a higher grade component in the RP is missed on the needle biopsy. A needle biopsy can also sample a tertiary higher grade pattern in the RP, which is then not recorded in the standard GS reporting, resulting in apparent overgrading on the needle biopsy. Almost 20% of our RPs had a tertiary grade pattern that other articles analyzing the relationship between biopsy and RP GS do not account for [3]. Several scenarios with biopsy versus RP grade comparisons can be affected by the RP tertiary grade. A total of 11.2% of cases had GS 5–6 on biopsy with GS 6 plus tertiary at RP; 12.4% and 3.6% of cases had biopsy GS 3 + 4 = 7 and GS 4 + 3 = 7, respectively, with GS 6 plus tertiary at RP. If the tertiary grade patterns were not recorded, the explanation would have been overgrading of the biopsy as opposed to the biopsy sampling a small component of Gleason pattern 4. Similarly, a total of 18.5% of cases with biopsy GS 9–10 had RP with GS 3 + 4 or GS 4 + 3 with tertiary grade pattern 5; these cases would have been explained as due to pathology undergrading the biopsy had the tertiary grade pattern 5 in the RP not been recorded. In the cases where the biopsy does not show as high-grade cancer in the RP in addition to pathology error, it may reflect a sampling error even when the entire prostate is submitted for histologic analysis. A very focal high-grade component may not be identified in the RP when the high-grade component remains deeper within a paraffin block and not sectioned onto glass slides (only a 5-μm section is placed on a slide for every 3 mm of tissue within a paraffin block).

In reviewing the literature to determine the incidence of upgrading, we analyzed a number of series looking only at the incidence of upgrading from biopsy GS ≤6 to RP ≥7 with a minimum of 100 cases, where the cases studied ranged from 1992 to the present. Of the studies that fit these criteria, upgrading was seen in 3975 of 11 472 cases (35%) with a mean of 36% and a median of 35.5% (range: 14–51%) [6–20]. In the current study, the incidence of upgrading from ≤6 to ≥7 was 36.3%. Several quantifiable factors such as serum PSA values, pathology weight, age, extent of cancer on biopsy, and needle biopsy sampling can have an impact on the incidence of upgrading. One variable more difficult to quantify is the difference in experience and skill in grading among pathologists, although it has been shown that the needle biopsy and RP GSs more closely match when graded by urologic as opposed to general pathologists [1,21].

There are fewer studies examining the incidence of downgrading. Three studies looked at downgrading from GS 8−10 to ≤7 with results ranging from 29%, 40%, to 56% [15,17,22]. In the current study, 51.3% of GS 8 biopsies had a lower grade at RP. In cases with biopsy GS 9–10, 31.1% had RP grades ≤7. Moussa et al. recorded a 7.3% incidence of downgrading from GS 3 + 4 = 7 to GS ≤6 [14]. In the current study, 12.0% of cases diagnosed as 3 + 4 = 7 on biopsy had GS 5–6 at RP. One explanation for these cases is that tangentially sectioned small glands of pattern 3 on biopsy were overgraded as Gleason pattern 4. Alternatively, in some cases the assigned biopsy GS may have been accurate with such small foci of Gleason pattern 4 in the RP that it was either not recorded or unsampled deeper within the paraffin block. In cases with borderline GS 5–6 versus GS 3 + 4 = 7 on biopsy, it is probably better to diagnose the case as GS 6 because potential undergrading due to sampling error is more acceptable than overgrading due to grading error.

Numerous studies have demonstrated that extended biopsies, whether ≥10 or 12 cores, are associated with less upgrading than sextant biopsies with even less upgrading with saturation biopsies [16,23,24]. This highlights the importance of sampling error in the concordance of biopsy and RP GSs; however, it is less an issue in the current era because extended biopsies are the standard of care.

In almost all studies, age was not predictive of upgrading [8,15–17,25]. In the current study, although strongly statistically significant, the mean difference between those with and without upgrading was only 1.6 yr. In almost all prior studies, clinical stage was also not predictive, and in the few studies where it was predictive it was only weakly so [6,8,16,17,25]. The findings in the current study showed small but statistically significant increases in upgrading and decreases in downgrading in univariate comparisons with clinical stage, but these did not remain significant in multivariable analyses. In approximately three quarters of prior studies, serum PSA levels correlated with upgrading, although in several studies the relationship was weak [6–8,10–13,15–19,24,25]. The relationship with serum PSA level and upgrading in most studies held up in multivariable analysis. Higher PSA values are in general associated with larger RP tumor volume, and there is also a correlation between RP grade and tumor volume. Consequently, in cases with GS 6 on biopsy and higher PSA, there is an increased likelihood that a higher grade pattern in the RP was not sampled. The findings in the current study are in agreement with these prior works. One study in the literature demonstrated a relationship between percentage free PSA and upgrading [19]. Another report revealed no relationship between PSA velocity and upgrading [11]. Free PSA and PSA velocity were not assessed in the current work.

Enlarging prostate size was associated with less upgrading in about 70% of the publications on this issue [6,8,14,23, 25–28]. In our study, although there was progressively less upgrading with increasing prostate size up to 75 g, the most dramatic decrease in upgrading was seen in very large prostates (>75 g). There was also a relation to downgrading with increasing prostate size. As expected, given the relationship between increased serum PSA levels and decreased weight with upgrading, PSA density was shown to be even more correlated with upgrading than PSA alone [12,29].

The relationship between the extent of cancer on biopsy and upgrading was less consistent, with approximately 50% of the articles demonstrating a relationship [6,8–11,14, 17,18,20,24,25]. Both the number of positive cores and the maximum percentage of cancer per core were predictive in the current study. Higher maximum percentage of cancer was independently predictive of upgrading from biopsy GS 5-6 to GS≥7, and lower cancer extent on biopsy predicted downgrading biopsy GS 3 + 4 = 7 to GS 5–6 at RP. Large tumor volume on needle biopsy correlates with large tumor volume in the RP, which is correlated with increased RP GS. Consequently, although one would expect having a larger amount of cancer tissue available for pathologic analysis that the risk of upgrading would be lower, in cases with GS 6 on biopsy and with extensive cancer on biopsy, there is an increased likelihood that a higher grade pattern in the RP was not sampled. Although beyond the scope of this analysis, future studies may specifically examine tumor volume and location and subsequently provide a greater insight into the nature of discordance between biopsy and RP Gleason score.

Despite the large sample sizes in the current study, the discriminative power of the various models is somewhat modest, with all c-index values <0.70. Thus, although we had planned on deriving nomograms to predict upgrading and downgrading, it was considered that their predictability for individual patients would not be sufficiently accurate for clinical use. Additional limitations include the heterogeneity of biopsy indications, biopsy technique, and templates (although extended template biopsy is the standard of care during the time period of data acquisition). At our institution, most patients present with biopsies performed at outside facilities, and it is difficult to determine in many cases the number of sampled cores to determine the fraction of positive cores. Finally, future studies will correlate pathologic findings to biochemical recurrence and other outcomes as patients continue to be followed.

5. Conclusions

GS upgrading and downgrading remain an important issue using the updated Gleason system, even when accounting for tertiary Gleason patterns in the RP. Even in the setting of grading prostate cancer in a center with extensive prostate cancer pathology expertise, approximately a quarter of GS 5–6 tumors on biopsy will be GS 7 or higher at RP. Additional tools are needed to better predict upgrading and downgrading because the currently available standard clinical and pathologic variables are insufficiently predictive for clinical use.

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Table 1

Patient characteristics

Age, yr	
Mean	58.3
Median	58
Range	34–79
Prostate-specific antigen	
Mean	5.8
Median	4.7
Range	0.17–97.2
Clinical stage (%)	
≤T1c	5772 (75.5)
T2a	1238 (16.2)
T2b	360 (4.7)
T2c–T3	79 (1.0)
Biopsy Gleason score (%)	
5	6 (0.1)
3 + 3	5071 (66.3)
3 + 4	1577 (20.6)
4 + 3	615 (8.0)
8	261 (3.4)
9–10	119 (1.6)
No. of positive cores	
Mean	3.0
Median	2
Range	1–16
Maximum percentage of cancer per core	
Mean	43.7
Median	40
Range	1–100
Radical prostatectomy weight, g	
Mean	53.5
Median	49
Range	20–334

Table 2

Radical prostatectomy grades stratified by biopsy Gleason scores

Biopsy GS	5–6		3 + 4 = 7		4 + 3 = 7		8		9–10	
Radical prostatectomy GS	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
5–6	3230	(63.7)	190	(12.0)	33	(5.4)	3	(1.1)	4	(3.4)
3 + 3 + T	567	(11.2)	196	(12.4)	22	(3.6)	3	(1.1)	1	(0.8)
3 + 4 = 7	946	(18.7)	784	(49.7)	172	(28.0)	32	(12.3)	4	(3.4)
3 + 4 + T	70	(1.4)	74	(4.7)	26	(4.2)	16	(6.1)	5	(4.2)
4 + 3 = 7	152	(3.0)	201	(12.7)	174	(28.3)	49	(18.8)	6	(5.0)
4 + 3 + T	47	(0.9)	84	(5.3)	105	(17.1)	31	(11.9)	17	(14.3)
GS 8	26	(0.5)	25	(1.6)	25	(4.1)	56	(21.5)	6	(5.0)
GS 8 + T	11	(0.2)	4	(0.3)	25	(4.1)	24	(9.2)	7	(5.9)
GS 9–10	22	(0.4)	19	(1.2)	33	(5.4)	47	(18.0)	69	(58.0)
Total	5071	(100.0)	1577	(100.0)	615	(100.0)	261	(100.0)	119	(100.0)

GS = Gleason score; T = tertiary higher grade pattern.

For Gleason pattern 6, T refers to the presence of either tertiary pattern 4 or 5. For any Gleason pattern >6, T refers to tertiary pattern 5.

Table 3

Association of clinical and pathologic parameters with Cleason score (GS) group: upgrading from biopsy GS 5–6 to GS >6 at radical prostatectomy

Variables	Upgrade (*n*= 1841)	No upgrade (*n* = 3230)	*p* value
Age, yr			
Median (range)	59.0 (36.0–77.0)	57.0 (34.0–79.0)	
Mean (SD)	58.7 (6.4)	57.0 (6.5)	<0.0001
PSA, ng/ml			
Median (range)	5.1 (0.5–97.2)	4.5 (0.2–43.1)	
Mean (SD)	6.1 (4.4)	5.0 (3.1)	<0.0001
No. of positive cores			
Median (range)	2.0 (1.0–12.0)	2.0 (1.0–12.0)	
Mean (SD)	3.0 (2.2)	2.4 (1.8)	<0.0001
Maximum % cancer/core			
Median (range)	40.0 (1.0–100.0)	25.0 (1.0–100.0)	
Mean (SD)	43.6 (29.2)	33.7 (26.7)	<0.0001
Pathology weight (continuous)			
Median (range)	47.3 (11.7–198)	50.7 (12.2–254.0)	
Mean (SD)	50.4 (16.6)	55.9 (22.0)	<0.0001
Pathology weight (%)			
≤25 g	20 (43.5)	26 (56.5)	
26–50 g	967 (42.4)	1313 (57.6)	<0.0001
51–75 g	597 (37.3)	1005 (62.7)	
≥75 g	257 (22.5)	886 (77.5)	
Clinical stage (%)			
≤T1c	1110 (29.4)	3667 (70.6)	
T2a	240 (23.5)	779 (76.5)	0.006
≥T2b	105 (30.9)	235 (69.1)	

SD = standard deviation; PSA= prostate-specific antigen.

Table 4

Multivariate logistic regression models to predict radical prostatectomy (RP) Gleason score (GS) based on biopsy GS: (a) Prediction of upgrading from biopsy GS 5–6 to GS >6 at RP (*n* = 2688); (b) prediction of downgrading from biopsy GS 3 + 4 = 7 to GS 5–6 at RP (*n* = 943)

a.

Variable	OR (95% CI)	*p* value
Age, yr	1.057 (1.044–1.069)	<0.0001
PSA, ng/ml	1.113 (1.104–1.163)	< 0.0001
Maximum % cancer/core	1.010 (1.008–1.013)	<0.0001
Pathology weight	0.976 (0.972–0.981)	<0.0001
c-index of overall model: 0.685		

b.

Variable	OR (95% CI)	*p* value
PSA, ng/ml	0.930 (0.870–0.993)	0.031
Maximum % cancer/core	0.989 (0.983–0.996)	0.002
Pathology weight	1.010 (1.001–1.019)	0.019
c-index of overall model: 0.629		

OR = odds ratio; CI = confidence interval; PSA = pro state-specific antigen; c-index = concordance index.

Table 5

Association of clinical and pathologic parameters with downgrading from biopsy Gleason score (GS) 3 + 4 to GS 5–6 at radical prostatectomy

Variables	Downgrade (*n* = 190)	No downgrade (*n* = 1387)	*p* value
Age. yr			
Median (range)	60.0 (34.0–74.0)	60.0 (36.0–76.0)	0.538
Mean (SD)	58.9 (7.4)	59.2 (6.6)	
PSA, ng/ml			
Median (range)	4.8 (0.3–32.2)	5.1 (0.9–64.8)	
Mean (SD)	5.5 (3.3)	6.4 (5.2)	0.028
No. of positive cores			
Median (range)	3.0 (1.0–11.0)	4.0 (1.0–14.0)	
Mean (SD)	3.5 (2.4)	4.1 (2.5)	0.006
Maximum percentage of cancer per core			
Median (range)	40.0 (5.0-100.0)	60.0 (5.0–100.0)	<0.0001
Mean (SD)	48.0 (29.7)	57.3 (28.6)	
Pathology weight (continuous)			
Median (range)	47.8 (15.9-152.0)	46.3 (21.3–333.8)	0.025
Mean (SD)	53.9 (19.8)	50.1 (19.8)	
Pathology weight (%)			
≤25 g	1 (6.2)	15 (93.8)	
26–50 g	82 (9.3)	798 (90.7)	<0.0001
51–75 g	47 (11.1)	377 (88.9)	
>75 g	60 (23.3)	197 (76.7)	
Clinical stage (%)			
≤T1c	132 (14.7)	766 (85.3)	
T2a	47 (13.0)	314 (87.0)	0.025
≥T2b	6 (5.4)	105 (94.6)	

SD = standard deviation: PSA= prostate-specific antigen.